Revised manuscript. Article published in Chem. Eur. J. ***2016****, 22, 144 – 152 (doi: 10.1002/chem.201503742)*

Stereoselective synthesis of 1,3-diaminotruxillic acid derivatives: an advantageous combination of C–H-*ortho*-palladation and on-flow [2+2]-photocycloaddition in microreactors

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Abstract

The stereoselective synthesis of ε-isomers of dimethyl esters of 1,3-diaminotruxillic acid in three steps is reported. The first step is the orthopalladation of (*Z*)-2-aryl-4-aryliden-5(4*H*)-oxazolones **1a**–**t** to give dinuclear complexes **2a**–**t** with bridging carboxylates. The reaction occurs through regioselective activation of the *ortho*-CH bond of the 4-arylidene ring in carboxylic acids. The second step is the [2+2]-photocycloaddition of the C=C exocyclic bonds of the oxazolone skeleton in **2a**–**t** to afford the corresponding dinuclear orthopalladated cyclobutanes **3a**–**t**. This key step was performed very efficiently using LED light sources with different wavelengths (465, 525 or 625 nm) in flow microreactors. The final step involved the depalladation of **3a**–**t** by hydrogenation in methanol to afford the ε-1,3-diaminotruxillic acid derivatives as single isomers.

Introduction

Truxillic and truxinic acid derivatives (Figure 1) have been known for more than a century.[1] In 1888 Liebermann characterized two isomers of truxillic acid among the decomposition products of cocamine,[2a-c] an extract obtained by Hesse from *Erythroxylum Coca* leaves in 1887.[2d] This type of compound quickly attracted the interest of a broad range of scientists due to their outstanding pharmacological and biological properties. Among many other properties, it is worth highlighting their remarkable antinociceptive (reduction of the sensitivity to painful stimuli by blocking the transmission of electrical signals)[3] and antimuscarinic[4] activities, even at low doses. In a different biological target, a specific class of truxillic acids, namely diaminotruxillic acid derivatives (Figure 1), have very recently been identified as the only non-peptidic agonists of GLP-1R (Glucagon-Like Peptide 1 Receptor), which is involved in the treatment of type 2 diabetes mellitus.[5] As a consequence, the high added value of these bioactive compounds is evident.

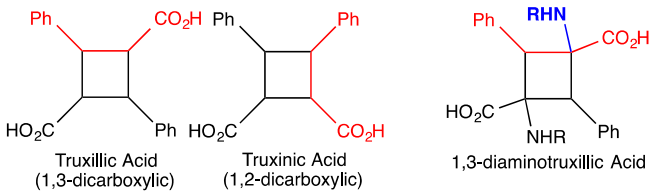

Figure 1. General representation of truxillic and truxinic acids.

The properties and applications outlined above prompted extensive research aimed at developing a simple and large-scale method to synthesize truxillic acids and their derivatives. In this respect, it is well known that the best method for the preparation of truxillic acid itself is the solid-state [2+2]-photodimerization of cinnamic acid under irradiation with UV light (Figure 2a).[6] Using the same approach, a retrosynthetic analysis leads to the conclusion that the [2+2]-photocycloaddition of the well-known and synthetically accessible (*Z*)-4-aryliden-5(4*H*)-oxazolones could provide a very plausible synthetic pathway (Figure 2b).[7]

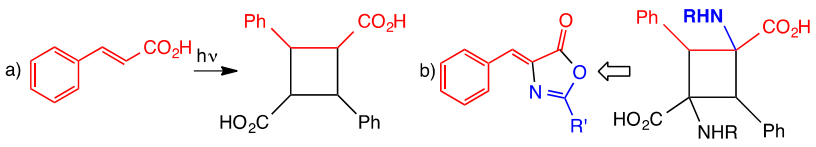

Figure 2. a) Synthesis of truxillic acid by [2+2]-photocycloaddition of cinnamic acid and b) proposed retrosynthesis of 1,3-diaminotruxillic acid derivatives.

Despite the chemical versatility of 5(4*H*)-oxazolones, access to truxillic acid derivatives from oxazolones is still difficult and is really quite limited. In this respect, the photochemical step is the bottleneck in the process. Previous reports on the photoirradiation of free 5(4*H*)-oxazolones in

solution cover a variety of processes (see Figure 3), which include the formation of diazetidines by [2+2] photocycloaddition of the C=N bonds,[8] (*Z*) to (*E*) isomerization[9] and, in only a single example, a [2+2]-photodimerization.[5d] The latter process takes place with a very poor efficiency since long reaction times (3 days) and strong irradiation (500 W) of the starting oxazolones are required to achieve a very low yield of the corresponding cyclobutanes (typically 10–15%).[5d] An additional problem is that the diaminotruxillic acid species' are obtained as a mixture of at least four different isomers, which must be separated by tedious HPLC separations before determination of their pharmacological and biological properties.[5d] Solid-state irradiation of samples in the crystalline state (as reported, for instance, for cinnamic acid) has been used as a method to limit the number of isomers.[6,10] However, these reactions are controlled by the crystal packing of the reacting molecules and, unless certain topochemical conditions are met (the C=C double bonds must be located in parallel planes, point in the same direction and have an intermolecular distance shorter than 4.2 Å) the process is not efficient.[10] Other synthetic routes are available to prepare cyclobutanes and these include the transition metal-mediated C–H functionalization of preformed cyclobutanes.[11] Despite very recent impressive developments, these reactions are still synthetically complex because they involve the C(sp^3)–H bond, which is difficult to activate, the need for precise chelating directing groups and they require careful control of the newly formed stereocenters.

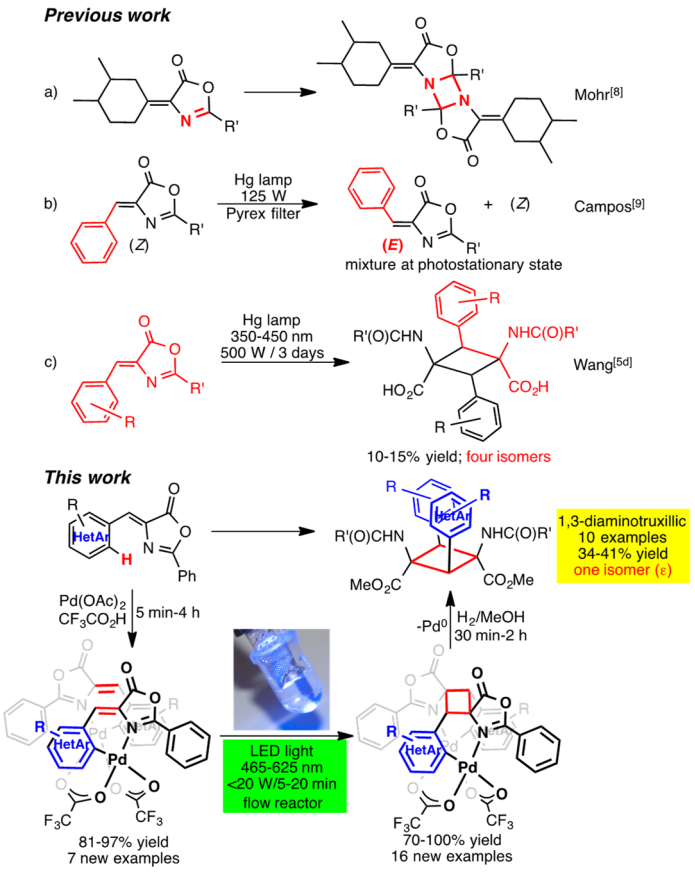

Figure 3. Previous work on the irradiation of oxazolones and comparison with the work here described.

We report here an efficient method for the synthesis of 1,3-diaminotruxillic acid derivatives based on a novel approach (see Figure 3). The first step is the orthopalladation of (*Z*)-2-aryl-4-(het)arylidene-5(4*H*)-oxazolones. We recently studied this reaction in depth in 4-arylidene systems and showed that this process only takes place with carboxylic acids and is regioselective at the ortho-CH bond of the arylidene ring.[12] In the present work the orthopalladation of 4-hetarylidene-5(4*H*)-oxazolones was achieved with the same regioselectivity, thus showing the broad scope of the process. The resulting dimeric orthopalladated complexes are especially suited to undergo, in a second step, the [2+2]-photocycloaddition process due to their clamshell structure. This structure behaves as a molecular template and locates the two C=C bonds in close proximity, thus favoring their interaction.[12a] In this work we present a very efficient methodology based on the irradiation of samples in solution with LEDs as a light source combined with flow microreactors.[13] In this way yields of 100% were obtained for the [2+2]-photodimerized products in reaction times as short as 5–20 minutes using low-energy input, long lifetime and inexpensive light sources, namely LEDs. In addition, the rigid environment in which the palladated oxazolones are located during the photocycloaddition step promotes the stereoselective formation of the cyclobutane ring and the synthesis of the corresponding palladated truxillic acid derivatives as a single isomer (ε-truxillic) in solution. The liberation of the ε-1,3-diaminotruxillic acid derivatives occurs smoothly in a third step after treatment of the [2+2]-photodimerized complexes with H_2 in methanol. Thus, this methodology overcomes all of the problems found in the literature for the photocycloadditon of free oxazolones (low yields, long reaction times and the presence of several isomers) and affords ε-1,3-diaminotruxillic acid derivatives with a remarkably broad scope of application.

Results and Discussion

1.- Orthopalladation of (*Z*)-2-aryl-4-hetaryliden-5(4*H*)-oxazolones.

The starting oxazolones (**1a**–**1t**) used in this work (see Figure 4) were prepared by literature methods (see Supporting Information for details). Complexes **1a**–**1m** have been reported previously.[12]

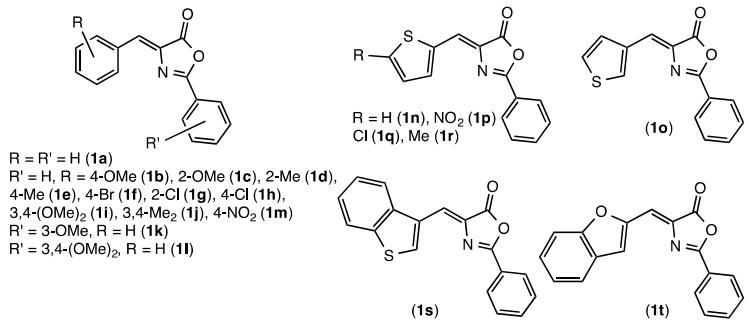

Figure 4. Oxazolones employed as starting materials in this work.

The orthopalladation of oxazolones **1n**–**1t** derived from heterocycles was carried out by treatment with $Pd(OAc)_2$ (1:1 molar ratio) in CF_3CO_2H as solvent (see Figure 5). In most cases the reaction took place at room temperature in short reaction times and only in the cases of nitro- (**1p**) and benzothiophene (**1s**) derivatives was heating necessary to achieve complete conversion. The corresponding orthopalladated dimers **2n**–**2t** were obtained in very good yields as air-stable solids. In general, the orthopalladation of hetarylidene-oxazolones **1n**–**1t** occurs under milder reaction conditions and shorter reaction times than for the corresponding arylidene-oxazolones **1a**–**1m** bearing the same substitutents. For instance, orthopalladation of unsubstituted 4-benzylidene-oxazolone (**1a**) required heating at 75 ºC for four hours to obtain a 64% yield of the isolated product **2a**,[12b] while orthopalladation of thiophene derivative **1n** occurred at room temperature in only five minutes to give **2n** in 95% yield. The same conclusions can be drawn by comparison between arylidene-oxazolones containing electron-releasing or electron-withdrawing groups and the corresponding heterocyclic derivatives. Therefore, the electronic nature of the ring is important for the outcome of the reaction, but it is not critical, and favors palladation of the electron-rich heterocyclic rings.

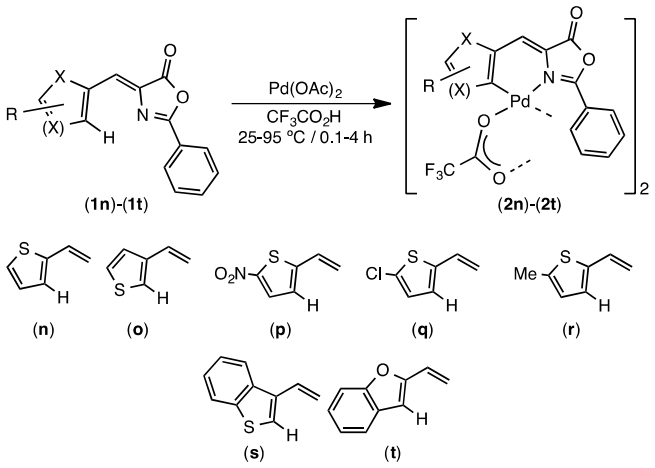

Figure 5. Regioselective orthopalladation of (*Z*)-2-phenyl-4-hetarylidene-5(4*H*)oxazolones **1n**–**1t**.

The characterization of **2n**–**2t** was carried out by conventional techniques. The analytical data are consistent with a dinuclear structure. The NMR data suggest that CH bond activation occurred at the heterocyclic ring to afford a six-membered palladacycle in all cases. Thus, the orthopalladation of 4-hetarylidene oxazolones **1n**–**1t** shows the same regioselectivity as the 4-arylidene systems **1a**–**1m**.[12b] In addition, the ease of palladation of the 3-position of the thiophene ring in **1n**, **1p**, **1q** and **1r** is remarkable because this is not the 'natural' reactivity of the thiophene ring. This seems to be a consequence of the *N*-directing effect. Finally, we suggest for complexes **2n**–**2t** a dimeric clamshell structure (Figure 5), with a relative head-to-tail arrangement of the two palladated oxazolones (C_2 symmetry), because only a single peak is observed in the ^{19}F NMR spectrum and due to similarities with closely related complexes that have fully determined X-ray diffraction structures.[12b]

2.- [2+2]-photocycloaddition processes in flow reactors.

Previous work by our group showed that $CDCl_3$ solutions of some orthopalladated complexes (**2a**, **2k**, **2l**) evolved to give the product of a [2+2]-cycloaddition when exposed to sunlight.[12a] This procedure has clear advantages over other reported [2+2]-cycloadditions:[5d] (i) the reaction occurs with complete conversion to a single compound and (ii) full stereoselectivity is obtained due to molecular constraints. The [2+2] photo-cycloaddition of the orthopalladated complexes **2a**–**2m**[12b] and **2n**–**2s** was studied. In the first step we screened the range of reaction times required for complete conversion (where possible) of **2a**–**2s** into **3a**–**3s** upon irradiation with sunlight in $CDCl_3$ solution. The results are collected in Table 1 and it can be seen that the times required for complete conversion range from 28 h to 480 h. It is clear that this is not an efficient process. In some other cases the cycloaddition was only partial or was not observed at all. Since the reactions were performed in NMR tubes, only small amounts of samples (milligrams) were obtained in each case and attempts to scale-up the process were unsuccessful. In addition, the free truxillic acid derivatives were not obtained. In an effort to overcome these problems and to define a highly efficient process with the widest scope, a different methodology based on the combined use of microreactors and flow chemistry was developed. This approach has the advantages of both fields. On the one hand, the high surface-to-volume ratio of microreactors allows the effective transmission of light through the reaction mixture, thus favoring diffusion and mass transfer to provide enhanced reaction efficiency and safety.[13c] On the other hand, the use of continuous flow allows good control of reaction conditions, which minimizes product photodegradation. The general process is shown in Figure 6 and the results are listed in Table 1.

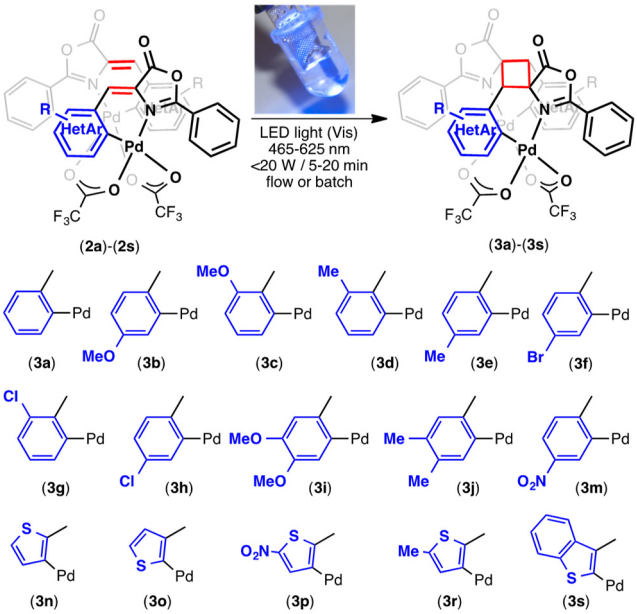

Figure 6. [2+2]-cycloaddition of orthopalladated oxazolones.

Table 1. Optimization of the [2+2]-photocycloaddition of orthopalladated complexes (**2a**)-(**2s**)

Entry	Compound	*t* (h)[a]	conversion (%)[b]	*t* (h)[c]	conversion batch (%)[d]	conversion in flow (%)[d]			
						white	blue	green	red
1	**2a**	28	100	0.5	81 (red)	80 (0.33)	85	86	96
2	**2b**	480	75	0.33	100 (blue)	100	100	90	0
3	**2c**	432	100	0.5	100 (blue)				
4	**2d**	240	100	0.33	100 (blue)		100		
5	**2e**	72	100	0.33	98 (blue)		90		
6	**2f**	72	100	0.33	100 (blue)	88	100	68	6
7	**2g**	432	100	0.5	100 (blue)	70	100		
8	**2h**	192	100	0.5	100 (blue)				
9	**2i**	480	0	0.33	70 (white)	100	45	54	0
10	**2j**	120	100	0.5	56 (blue)	52 (0.33)[e]	90	62	0
11	**2m**	380	100	0.5	100 (blue)				
12	**2n**	480	0	0.33	34 (blue)	20	52	40	4
13	**2o**	480	0	0.5	70 (white)	30	58	49	0
14	**2p**	480	0	0.16	100 (blue)	100	100	94 (0.33)[e]	0
15	**2r**	480	0	0.33	0 (white)	100	0	0	0
16	**2s**	480	0	0.5	22 (green)	0	0	20	0

[a] irradiation time using sunlight. [b] conversion of substrate **2** into product **3** achieved during the time specified in [a]. [c] irradiation time using LEDs as the light source. [d] conversion of substrate **2** into product **3** achieved during the time specified in [c]. [e] irradiation time was 0.33 h instead of 0.16 h.

Our approach employed a microreactor that consisted of a coil of fused silica capillary placed on top of a light source. The total length of the capillary was 1.9 m (internal diameter of 100 μm), which resulted in a reaction volume of 15 μL. The light source consisted of a collection of 28 light-emitting diodes (LED) placed on a printed circuit board (PCB) (see Supporting Information for more details of the experimental setup). The reaction volume was directly illuminated by the PCB of LEDs. LEDs have recently become the energy saving light source of choice in many applications[13c] and they are available in a wide range of wavelengths.[14] Thus, the solutions of the corresponding orthopalladated derivatives **2a**–**2s** in $CDCl_3$ (6 mM) were pumped through the capillary while being irradiated by the LED printed board. The residence time was controlled by the flow rate of a Harvard syringe pump. In order to optimize the absorption of energy for each individual compound, four different wavelengths were tested on each sample: blue (465 nm), green (525 nm), red (625 nm) and white (405–700 nm) and for different residence times (10 min,

20 min, 30 min) by simply changing the flow rate accordingly. The reaction mixture (around 100 μL) was collected in a vial, transferred to a 5 mm NMR tube and diluted with 400 μL of $CDCl_3$. The progress of the reaction was monitored by ^1H NMR experiments on the reaction mixture at different times, with the aim of determining the maximum conversion achieved for each wavelength and for each residence time. The reaction conditions that afforded the best conversions in continuous flow were subsequently transferred to batch mode using a 5 mm NMR tube as the reaction vessel. The mixture was directly illuminated by the same system of LEDs.

It can be seen from the data in Table 1 that the improvement in the efficiency of the reaction was outstanding in two different respects. Firstly, the acceleration experienced by reactions that already took place under sunlight irradiation but required days (even weeks) to reach completion, which was the case for most complexes. As a representative example, compound **2a** required 28 hours under sunlight for complete conversion into **3a**, as reported previously.[12a] On applying the methodology developed here, the irradiation of **2a** (entry 1) under flow conditions with red LED lamps afforded a clean and virtually complete transformation of **2a** into **3a** as the only product in reaction times as short as 30 minutes. It is clear that, although the best result was obtained using red light, the compound is sensitive to changes in wavelength because high conversions (≥ 80%) were also achieved with white, blue or green lights during the same period. On the other hand, the enhancement of the reaction under the continuous flow regime is clear: 81% conversion in batch vs 96% in continuous flow with red light (625 nm).

Huge accelerations were also observed for **2c**–**2h** and **2m** (Table 1), for which complete conversions into the corresponding photocycloaddition dimers **3c**–**3h** and **3m** were achieved on using blue light (465 nm) under either flow or batch conditions. In these cases (entries 3–8 and 11) the reaction times were reduced from up to 18 days to barely 10–30 minutes. In the case of **2j** (entry 10) a lower conversion to **3j** was obtained but this was still as high as 90%. The transfer of the optimized flow conditions to batch conditions did not lead to significant changes and complete conversions were also obtained in minutes, again with the exception of **2j**. It is noteworthy that the progress of the reaction seems to be independent of the nature and position of the substituents, because very similar conversions were obtained in quite similar reaction times when electron-donating (Me in **2d** or **2e**, OMe in **2b**) or electron-withdrawing (Br in **2f**, Cl in **2g** and **2h**, NO_2 in **2m**) substituents were present in *ortho*- and *para*-positions.

In order to assess the stability in solution of the photo-cycloaddition dimers **3a**, **3c**–**3h**, **3j** and **3m**, further NMR measurements were carried out on the corresponding solutions for several hours after irradiation had finished. For the aforementioned complexes a reversal of the photocycloaddition was not observed under those conditions as signals due to the starting compounds were not detected during the monitoring time. As a representative example (Figure S2), a set of ^1H NMR spectra for complex **3g** taken every hour after irradiation had finished is presented in the Supporting Information. The absence of new signals due to **2g** in these spectra shows that **3g** is stable in solution.

The marked decrease in the reaction time needed to reach maximum conversions could be due to two factors, namely the selection of the wavelength and the large increase in the surface/volume ratio, as is usual for flow conditions, in comparison with a 5-mm NMR tube.[13-15] Although it is difficult to quantify the contribution of each of these factors to the substantial decrease in the time needed to reach full conversion, it seems that the correct choice of the wavelength is more critical. In fact, once the reaction had been optimized under flow conditions it was possible to transfer the conditions to a batch reactor without a detrimental effect on the conversion. Note that there are still several reactions that proceed with higher conversions when working under continuous flow (**2a**, **2i**, **2j**, **2n**) than under batch conditions. It is worth mentioning that the optimization of the reaction conditions in continuous flow is less time-consuming and cheaper than for the batch conditions and this justified the approach followed.

The second remarkable improvement achieved with this system concerns reactions that did not undergo complete [2+2]-photocycloaddition upon irradiation with sunlight, or those that did not proceed at all regardless of the exposure time used. This is the case for complexes **2b**, **2i** and **2n**–**2s**, with some notable differences observed between them. In the case of complex **2b**, a mixture of **2b/3b** (1/3 molar ratio) was obtained after exposure to sunlight for 20 days. This molar ratio could not be improved upon further exposure. Notably, irradiation of **2b** with either blue (465 nm) or white LED lamps under flow conditions with a residence time of only 20 minutes led to complete photocycloaddition and 100% conversion of **2b** into **3b**. A conversion of 90% was even observed on using green light (525 nm) with the same residence time. Moreover, irradiation of **2b** with blue light under batch conditions also led to complete transformation into **3b** in only 20 minutes. Therefore, not only is it possible to accelerate the reaction, but the method also provides access to compounds that cannot otherwise be made.

More impressive are the cases of complexes **2i** and the whole set of 4-hetarylidene derivatives **2n**–**2s**, because in these cases conversion was not detected at all even after exposure to sunlight for periods as long as 20 days (Table 1, entries 9 and 12–16). For complex **2i**, 100% conversion into **3i** was achieved on using white LED light under flow conditions in only 20 minutes, while 70% conversion was observed in batch under the same irradiation conditions (entry 9). In addition, partial transformation of **2i** into **3i** was observed on using blue (45%) and green (54%) LED lights, whereas the cycloaddition did not take place on using red light. For complexes **2n** and **2o** partial conversions were observed under both flow and batch conditions, with **2n** proving to be more sensitive to the blue light (maximum conversion 52%) and **2o** to white light (maximum conversion 70%). Fortunately, better results were obtained for the 5-substituted thiophenes regardless of the electron-releasing or electron-withdrawing nature of the substituent. For example, 5-nitro derivative **2p** underwent the [2+2]-photocycloaddition with 100% conversion into **3p** on using blue light, both in flow and in batch conditions, with a reaction time of only 10 minutes. Excellent results were also obtained when **2p** was irradiated with white light (100% conversion). In the case of the 5-methyl derivative **2r**, 100% conversion into **3r** was observed after 20 minutes irradiation with white light under flow conditions, but the reaction did not proceed at all in batch

mode. Finally, the presence of a benzo moiety fused to the thiophene group seemed to deactivate the system, because only 22% conversion was observed for **2s** on using green light.

The stability of the last set of complexes (namely **3b**, **3i** and **3n**–**3s**) in solution was assessed and it was found that the stability is somewhat limited. As mentioned above, the control of the reverse reaction was evaluated by measuring the ^{1}H NMR spectra of the solutions of complexes of type **3** at regular intervals for several hours after irradiation had finished, i.e., after maximum conversion had been attained (see examples in the Supporting Information). In this way, it was established that complex **3b** reverted completely to **2b** in approximately 12 hours (Figure S1 in Supporting Information), while complex **3i** reverted to **2i** in around 24 hours. This finding is a drawback for this method since it limits to some extent the scope of accessible 1,3-diaminotruxillic acid derivatives. This reversal is more severe in the case of heterocyclic derivatives **3n**–**3o**. As shown in Figures S3 and S4 in the Supporting Information, the time required for complete reversal of **3n** to **2n** is around 98 minutes, whereas that for **3o** to **2o** is around 24 hours. It is likely that the reversal of the [2+2]-photocycloaddition is closely related to the long times required for the reaction promoted by sunlight for these derivatives.

The outstanding efficiency of the present system based on LED irradiation and flow conditions in microreactors with high surface-to-volume ratios is clear, because a significant improvement in the results was obtained in comparison to the use of sunlight and the approach allows easy access to compounds that are not attainable by other methodologies. The only drawback found to date is the reversal of the photocycloaddition in some cases. It seems that the presence of substituents of a different nature has a definite influence on the reaction outcome, but with the present data it is difficult to establish correlations.

3.- Liberation and characterization of ε-truxillic acid derivatives.

Once the experimental conditions for the [2+2]-photocycloadditions had been optimized and good yields of the photodimerized complexes **3a**–**s** had been obtained, we aimed to obtain the palladium-free 1,3-diaminotruxillic acid esters. In an effort to achieve this goal depalladation of complexes type **3** was attempted. For this task representative examples were selected from cases where the photocycloaddition had been shown to be irreversible, with the aim of avoiding the formation of byproducts derived from the presence of type-**2** complexes. Several methods can be used to induce depalladation but we have found that the best performance is achieved by treatment of solutions of **3a**–**3m** in methanol with molecular hydrogen. The hydrogenation process (see Figure 7) took place under mild conditions (room temperature, pH_2 = 1 atm) and in reaction times ranging from 30 minutes to 2 hours. After the reaction a simple filtration of the resulting suspension removes the Pd^0 and evaporation to dryness of the resulting solution afforded a mixture of two compounds. The major components of these mixtures correspond to the methyl esters of 1,3-diaminotruxillic acid derivatives **4a**–**4m'** (Figure 7), which were obtained in around

40% yield. The minor components of the mixtures were the phenylalanine derivatives **5a**–**5m'**, which were formed in small amounts, with typical yields around 5–10%.

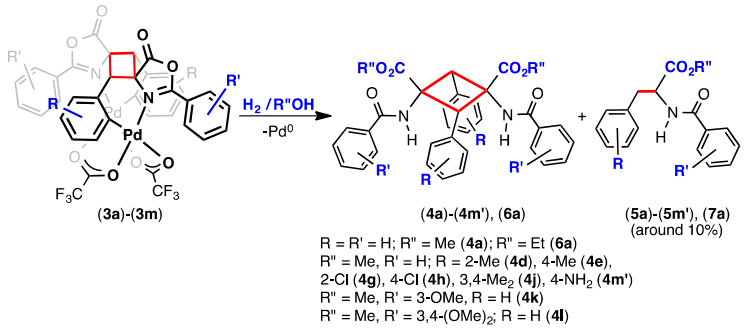

Figure 7. Depalladation of representative examples and liberation of alkyl esters of the 1,3-diaminotruxillic acids.

In general, the truxillic acid esters **4** can be easily separated from phenylalanines **5** by standard column chromatography using ethyl acetate/*n*-hexane mixtures. The only exceptions were the mixtures **4d/5d** and **4g/5g**, which proved to be difficult to separate by chromatography even after exhaustive screening of solvents. Also as a general rule, the hydrogenation tolerates well the presence of functional groups that are susceptible to hydrogenation, such as halogens or alkoxides. In this respect, excellent results were obtained with substituents such as 2-Cl (**4g**), 4-Cl (**4h**), 3'-OMe (**4k**) or 3',4'-$(OMe)_2$ (**4l**), which remained intact at the end of the reaction. However, hydrogenation of the 4-Br derivative (**3f**) occurred with concomitant dehalogenation and **4a** was obtained instead. Furthermore, the reaction of the 4-NO_2 derivative (**3m**) occurred with simultaneous depalladation and hydrogenation of the nitro group to afford the diamino compound **4m'** (Figure 7).

The synthesis of compounds **4a**–**4m'** as dimethyl esters means that not only had depalladation taken place by hydrogenation of the Pd–C bond, but that the resulting bis-oxazolone had also reacted with the solvent (MeOH) to give the methanolysis product by opening of the oxazolone ring. This dependence of the reaction product on the nature of the solvent was confirmed by performing the hydrogenation of complex **4a** in ethanol. In this case, the corresponding ethyl ester derivative (**6a**) was obtained. This finding is advantageous because it paves the way for the modular synthesis of 1,3-diaminotruxillic acid esters that are substituted not only on the phenyl rings, initially in the 4- and 2-positions, but also in the carboxylate and the amido functions. Not surprisingly, when the hydrogenation was carried out in aprotic solvents, regardless of their polarity (toluene, CH_2Cl_2 or THF), decomposition was observed but definite products could not be identified from the crude mixtures.

The formation of the phenylalanine derivatives (**5**) is particularly striking but it is not clear at which point they are formed. Firstly, these compounds were not detected in all cases. Secondly, the stability in solution of the type-**3** complexes was studied for several hours and it was confirmed

that reversal to type-**2** products did not occur in detectable amounts during these periods, which are longer than the time required for hydrogenation. For instance, the evolution of **3g** in solution was evaluated for 10 hours (Figure S3 in SI) and evidence for a retro-[2+2] reaction and formation of starting complex **2g** was not found. However, the hydrogenation of **3g** produced a mixture of **4g** and **5g**, as described above. Therefore, it seems unlikely that the presence of phenylalanines **5** should be due to the depalladation of complexes **2**, formation of the corresponding oxazolone **1** and hydrogenation of the oxazolone. Another possibility is the reversal of the diaminotruxillic acid derivatives **4** to the corresponding dehydrophenylalanines and subsequent hydrogenation in the presence of Pd^0 to give the phenylalanine. This also appears to be unlikely because the stability of representative examples of the truxillic acid derivatives (**4a**, **4d**, **4e**, **4m'**) was checked and evidence of further evolution of these species in solution was not found.

The characterization of the truxillic acid derivatives was carried out by standard spectroscopic and analytical methods (see Supporting Iinformation). Concerning the optical activity of these derivatives, the measurement of the optical rotation of a mixture of **4a/5a** gave a value of zero. This is expected bearing in mind that **4a** is achiral and that the hydrogenation takes place in the absence of chiral sources and, therefore, **5a** must be obtained as the racemic mixture.

Compounds **4a** and **5a** were also characterized by X-ray diffraction methods. Attempts to grow single crystals of each isolated compound **4** were unsuccessful. In contrast, crystals suitable for diffraction were obtained by crystallization of the crude mixture of truxillic acid derivative **4a** and the corresponding phenylalanine **5a**, i.e., the mixture obtained just after hydrogenation and removal of the Pd. The difficulties encountered in crystallizing each separate member were remarkable given that the mixture **4a/5a** crystallized easily. Two drawings of the co-crystallized mixture **4a/5a** are provided in the Supporting Information, along with a detailed analysis of the structure. A drawing of the ε-diaminotruxillic acid derivative **4a** is shown in Figure 8.

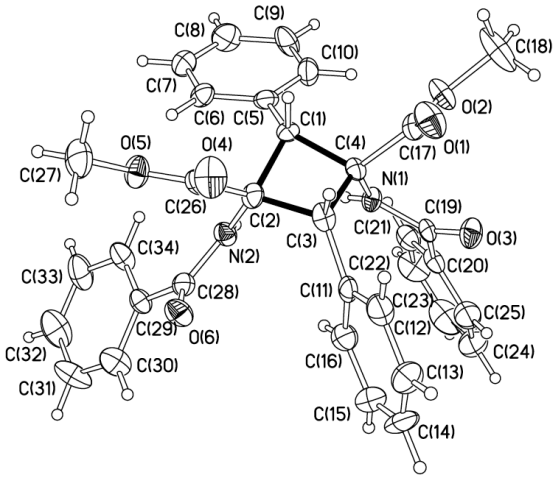

Figure 8. Drawing of the ε-diaminotruxillic acid derivative **4a**. Selected bond distances [Å] and angles [°]: N(1)–C(19): 1.349(4), N(1)–C(4): 1.437(4), N(2)–C(28): 1.361(4), N(2)–C(2): 1.458(4), O(1)–C(17): 1.198(4), O(3)–C(19): 1.240(4), O(4)–C(26): 1.203(4), O(6)–C(28): 1.217(4), C(1)–C(5): 1.506(5), C(1)–C(4): 1.563(4), C(1)–C(2): 1.567(5), C(2)–C(26):

1.540(5), C(2)–C(3): 1.568(4), C(3)–C(11): 1.499(5), C(3)–C(4): 1.559(4), C(4)–C(17): 1.534(5), C(19)–N(1)–C(4): 121.4(3), C(28)–N(2)–C(2): 119.8(3), C(5)–C(1)–C(4): 122.1(3), C(5)–C(1)–C(2): 122.6(3), C(4)–C(1)–C(2): 88.7(3), N(2)–C(2)–C(26): 110.5(3), N(2)–C(2)–C(1): 112.3(3), C(26)–C(2)–C(1): 113.9(3), N(2)–C(2)–C(3): 118.6(3), C(26)–C(2)–C(3): 112.9(3), C(1)–C(2)–C(3): 86.7(2), C(11)–C(3)–C(4): 122.6(3), C(11)–C(3)–C(2): 125.7(3), C(4)–C(3)–C(2): 88.8(3), N(1)–C(4)–C(17): 111.7(3), N(1)–C(4)–C(3): 115.0(3), C(17)–C(4)–C(3): 113.3(3), N(1)–C(4)–C(1): 114.2(3), C(17)–C(4)–C(1): 113.5(3), C(3)–C(4)–C(1): 87.2(3).

The mixture **4a/5a** crystallized in the orthorhombic space group $P2_12_12_1$, with one molecule of ε-diaminotruxillic (**4a**) and one N-benzoylphenylalanine derivative (**5a**) (i.e., one unit of the mixture) in the asymmetric part. This means that only one enantiomer of phenylalanine **5a** had crystallized together with the achiral **4a**. Given that the value of the optical rotation of the mixture **4a/5a** was determined to be zero, this unexpected spontaneous resolution could be explained as being due to a 'racemic conglomerate'.[16] Due to the absence of heavy atoms, it was not possible to determine unambiguously the absolute configuration of the Cα of the phenylalanine moiety.

It can clearly be observed from the structure of the diaminotruxillic acid derivative that it is the ε-isomer, which is consistent with the original assignment of isomers by Stoermer and Bachér.[17] Thus, the two carboxylate groups in positions 1 and 3 are in a *cis* disposition, as are the two phenyl rings in positions 2 and 4, while the phenyl rings and the carboxylate units are in mutual *trans* positions. This situation is clearly the result of a head-to-tail *syn*-dimerization of two (*Z*)-oxazolones, which is the same arrangement that was found for the orthopalladated cycloadducts **3**.[12a] This finding indicates that conformational changes had not occurred during the hydrogenation. The cyclobutane core is not planar and has a slightly folded structure. The out-of-plane dihedral angles C(1)–C(2)–C(3)–C(4) and C(2)–C(3)–C(4)–C(1) have values of –21.8(3)° and 21.9(3)°, which are similar to values found for other cyclobutane rings with these types of substituents.[5d,18] The two phenyl rings in the 2- and 4-positions are rotated by around 90° with respect to one another, and similar rotations were found in closely related structures.[5d] The phenylalanine unit **5a** forms strong H-bonds with the truxillic acid derivative **4a**, and this is probably one of the reasons for the easy co-crystallization. The H-bonds are established between the two NH protons of the truxillic acid derivative **4a**, which behaves as an H-donor, and the carbonyl oxygen of the amido group of the phenylalanine fragment **5a** as an H-acceptor. The parameters that define these H-bonds are as follows: For the N(1)–H(1A)···O(9) H-bond N(1)···O(9) = 3.110(5) Å, H(1A)…O(9) = 2.27 Å and N(1)–H(1A)–O(9) = 164.0°, while for the N(2)–H(2A)···O(9) H-bond N(2)···O(9) = 3.024(5) Å, H(2A)…O(9) = 2.17 and N(2)–H(2A)–O(9) = 169.6°, both corresponding to H-bonds of moderate strength, as defined by Steiner.[19] Finally, the internal parameters for bond distances and angles are as one would expect, with some deviations with respect to values found in the literature for similar bonding situations.[5d,20]

Conclusions

The stereoselective synthesis of a wide variety of 1,3-diaminotruxillic acid derivatives, as the ε-isomers, has been successfully accomplished starting from (*Z*)-4-(het)aryliden-2-aryl-5(4*H*)-oxazolones by an optimized three-step method. This procedure involves the regioselective orthopalladation of the oxazolones, the [2+2]-photocycloaddition of the orthopalladated complexes induced by irradiation with an LED light source, either in microreactors in continuous flow or under batch conditions, and the liberation of the truxillic acid derivatives as dialkyl esters by hydrogenation in alcoholic media. The reaction has a wide scope for 4-arylidene-oxazolones and tolerates substituents of different electronic nature at different positions of both the 4-arylidene and the 2-aryl rings. In all cases the reaction takes place in the range of hours and, due to the templating effect of the orthopalladation, it is stereoselective to the ε-isomer. All of these characteristics (wide scope, short reaction times and full stereoselectivity) represent improvements on the present availability of these types of compounds, which are of high added value due to their pharmacological activity. Limitations in the scope of the reaction are due to the reversal of the photochemical process. This aspect requires improvement and is currently under investigation.

The methodology developed here combines the advantages of microreactor devices with a continuous flow regime. It enables reproducibility, process reliability and a rapid preparation with minimum workup for a wide collection of photocycloaddition dimers. The high surface-to-volume ratio typical of microreactors (resulting in short diffusion paths) in combination with the optimum wavelength enhances the reaction in terms of reaction yields and reaction times when compared with direct irradiation with sunlight. This approach also enables access to several photocycloaddition dimers that cannot be obtained otherwise. The method described here permits rapid experimentation and scale-up, thus shortening the time from research to development and production, an interesting field considering the properties and applications of these truxillic acid derivatives. Scalability of this kind of reaction is simply a matter of pumping and irradiating the starting material with LEDs continuously through the microreactor. Once again, microreactor technology has enabled the development of a green and sustainable process with lower energy demands.[21]

Experimental Section

General methods: see Supporting Information for full details.

Synthesis of new orthopalladated complexes by C–H bond activation. The synthesis of **2n** is described here. All other compounds **2o**–**2t** are collected in the Supporting Information. To a solution of **1n** (232.1 mg, 0.91 mmol) in CF_3CO_2H (5 mL) was added $Pd(OAc)_2$ (205 mg, 0.91 mmol) and the resulting mixture was stirred at room temperature for 5 min. During this time an

orange solid precipitated. To this suspension was added distilled water (50 mL) and stirring was maintained for a further 15 min. The resulting orange precipitate was filtered off, washed with water (3 × 20 mL), dried *in vacuo* and characterized as **2n**. Yield: 420.4 mg (97%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 6.87 (d, ^{3}J = 5.1 Hz, 1H, SC_4H_2), 7.47 (t, ^{3}J = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.57 (s, 1H, $H_{7''}$), 7.61 (t, ^{3}J = 7.5 Hz, 1H, $H_{4'}$), 7.72 (d, ^{3}J = 5.1 Hz, 1H, SC_4H_2), 7.93 (d, ^{3}J = 7.3 Hz, 2H, $H_{2'}$, $H_{6'}$), ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$) δ: 120.6 (C), 122.6 (C), 127.2 (C), 128.6 (CH), 129.4 (CH), 131.0 (CH), 133.2 (CH), 133.6 (CH), 134.8 (CH), 137.3 (C), 160.6 (C), 168.0 (C). ^{13}C signals assigned to the CF_3CO_2 ligand were not observed. ^{19}F NMR (376.50 MHz, $CDCl_3$) δ: –74.75. IR (ν, cm^{-1}): 1789 (C=O), 1662 (C=C), 1625 (C=N). Anal. Calc for $C_{32}H_{16}F_6N_2O_8Pd_2S_2$: C, 40.57; H, 1.70; N, 2.96; S, 6.77. Found: C, 40.61; H, 1.61; N, 2.87; S, 6.73.

[2+2]-Photocycloaddition of orthopalladated complexes. The synthesis of **3d** is described here. All other compounds (**3a**–**3s**) are collected in the Supporting Information. Optimized procedure using a continuous flow microreactor and LEDs as the light source: A solution of orthopalladated **2d** (6 mM in CDCl3) was pumped through a fused silica capillary with a residence time of 20 min. The capillary coil was irradiated during this time with a collection of blue LEDs (465 nm) placed on a Printed Circuit Board. The irradiated solution was collected in a small vial. Evaporation of the solvent gave **3d** in quantitative yield. 1H NMR (400.13 MHz, $CDCl_3$) δ: 2.22 (s, 3H, CH_3), 5.36 (s, 1H, $H_{7''}$), 6.76–6.84 (m, 2H, $H_{5''}$, $H_{6''}$), 6.98 (d, ^{3}J = 7.6 Hz, 1H, $H_{4''}$), 7.69 (t, ^{3}J = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.78 (t, 1H, ^{3}J = 7.9 Hz, $H_{4'}$), 9.16 (d, 2H, $H_{2'}$, $H_{6'}$). ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$) δ: 20.97 (CH_3), 56.40 (CH), 70.35 (C), 122.27 (C), 126.96 (CH), 127.20 (C), 128.00 (CH), 129.47 (CH), 130.89 (CH), 131.66 (CH), 136.07 (C), 136.10 (CH), 137.58 (C), 168.54 (C), 174.07 (C). ^{19}F NMR (376.50 MHz, $CDCl_3$) δ: –75.22. IR (ν, cm^{-1}): 1837 (C=O), 1655 (C=N). MS (MALDI^{+}) m/z, (rel. int. %): 368.0 (21.4%) [M/2 – CF_3COO^{-}]$^{+}$. Anal. Calc. for $C_{38}H_{24}F_6N_2O_8Pd_2 \cdot 1/3CDCl_3$ (1003.25): C, 45.85; H, 2.44; N, 2.79. Found: C, 45.83; H, 2.43; N, 2.75.

Synthesis of ε-1,3-diaminotruxillic derivatives. The synthesis of **4a** is described here. All other compounds **4d**–**4m'** are collected in the Supporting Information. A yellow solution of **3a** (0.204 g, 0.22 mmol) in MeOH (20 mL) was stirred under a H_2 atmosphere for 30 min. After the reaction was complete the black suspension was filtered through a pad of Celite and the resulting colorless solution was evaporated to dryness to afford a mixture of aminotruxillic acid derivative **4a** and phenylalanine **5a** (6.7/1 molar ratio), which were separated by silica gel chromatography using ethyl acetate/n-hexane (40:30) as eluent. The first colorless band collected corresponded to compound **5a**. Further elution using the same eluent allowed the isolation of aminotruxillic acid derivative **4a**. Compound **4a** crystallized with a molecule of ethyl acetate, the presence of which was determined by ^{1}H NMR spectroscopy. The crystals were used for analytical purposes. **4a**, white solid, yield 46.3 mg (37%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 7.30 (t, ^{3}J = 7.3 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.32 (m, 1H, $H_{4''}$), 7.37 (t, ^{3}J = 7.8 Hz, 2H, $H_{3'}$, $H_{5'}$),

7.45 (t, ^3J = 7.8 Hz, 1H, $H_{4'}$), 7.52 (d, 2H, $H_{2''}$, $H_{6''}$), 7.57 (d, 2H, $H_{2'}$, $H_{6'}$), 7.92 (s, broad, 1H, NH). $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$) δ: 50.83 (CH), 53.51 (CH_3), 62.81 (C), 126.98 (CH), 127.80 (CH), 128.61 (CH), 128.70 (CH), 128.80 (CH), 131.79 (CH), 133.03 (C), 133.79 (C), 167.24 (CON), 172.87 (CO_2). IR (ν, cm^{-1}): 3283 (NH), 1735, 1660 (C=O). MS (ESI^+) *m*/*z*: 563.2 $[M + H]^+$. Anal. Calc. for $C_{34}H_{30}N_2O_6 \cdot EtOAc$ (650.3): C, 70.14; H, 5.89; N, 4.31. Found: C, 70.02; H, 5.86; N, 4.41. **5a**, pale yellow solid, yield 13.7 mg (11%). ^1H NMR (400.13 MHz, $CDCl_3$) δ: 3.26 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 5.10 (m, 1H, CH), 6.59 (broad s, 1H, NH), 7.14 (m, 2H, H_m, CH_2Ph), 7.07–7.50 (m, 3H, H_o+H_p, CH_2Ph), 7.43 (t, ^3J = 7.5 Hz, 2H, H_m, COPh), 7.50 (t, ^3J = 7.4 Hz, 1H, H_p, COPh), 7.72 (d, 2H, H_o, COPh). IR (ν, cm^{-1}): 3318 (NH), 1735, 1637 (C=O). MS (ESI^+) *m*/*z*: 284.4 $[M + H]^+$.

X-ray crystallography: Crystallographic data (excluding structure factors) for the structure of **4a**/**5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1401532. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). For specific experimental details, see SI.

Acknowledgements

Funding by the Ministerio de Economia y Competitividad (MINECO) (Spain, Projects CTQ2011-22589, CTQ2011-22410 and CTQ2013-40855-R, CTQ2014-54987-P) and Gobierno de Aragón-Fondo Social Europeo (Spain, groups E40 and E97) is gratefully acknowledged. M. V. G. thanks the Ministerio de Economia y Competitividad (Spain) for funding her contract through the Ramón y Cajal program and Parque Científico y Tecnológico de Castilla-La Mancha.

Keywords: azlactones • C-H bond activation • Photochem. React. • flow techniques • palladium

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