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Highly selective intermolecular Heck reaction for the soluble polymer supported synthesis of glutamic acid analogues

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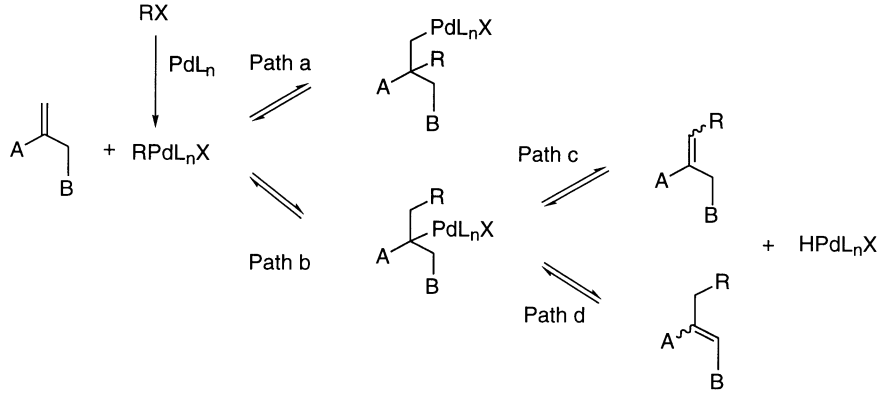
Abstract—Analogues of the neurotransmitter glutamic acid were synthesized by performing a Heck reaction on 4-methylene glutamic acid analogue. This reaction has proved to be highly regio- and stereoselective in the formation of trisubstituted olefin derivatives. A soluble polymer supported substrate yielded similar results and provided an efficient method for the parallel synthesis of novel glutamic acid derivatives. Furthermore a one-pot Pd-catalyzed alkylation/Heck arylation sequence has been developed. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The Heck reaction has become a basic tool in organic synthesis for the formation of C–C bond. It has proved to be versatile for the generation of new molecules and seems to provide endless application in organic chemistry.[1] However, one of the major drawback of this reaction is the lack of selectivity when it is carried out in its intermolecular version with unsymmetrical olefin such as 1,1-disubstituted alkenes. The arylation of these olefins is still a challenge because of their low reactivity and poor selectivity. The expected product is usually obtained as a mixture of regio- and stereoisomers, all the more so if one substituent of the alkene owns a substituent with a β-eliminable hydrogen (Scheme 1).[2–9] Regiochemistry of the addition of RPdLnX does not generally cause a problem since *path a* generates a neopentyl palladium species which cannot β-eliminate and, in the absence of a subsequent process involving palladium,[10] cannot regenerate the catalytic palladium. *Path b* generates a Pd complex which has two possibilities for β-elimination either via *path c* to yield the 'classical' Heck reaction product or via *path d*. In both cases a selectivity problem arises for the stereochemical outcome of the reaction. Consequently such a process may yield four different isomers.

During our search of new methods for the synthesis of glutamic acid analogues, we investigated the possibility of performing a Heck reaction on the side chain of a glutamic acid derivative[11] owning a 1,1-disubstituted olefin. These derivatives may serve as pharmacological tools for the exploration of the central nervous system.[12] As part of our



Scheme 1.

Keywords: poly(ethylene glycol); supported synthesis; palladium; Heck reaction; glutamic acid.
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involvement in the synthesis of aminoacid derivatives supported on a soluble polymer,[13] we also considered developing this reaction on a poly(ethylene glycol) (PEG) supported substrate. Liquid phase organic synthesis (LPOS)[14] where soluble polymers such as PEG are used as polymeric support is a practical alternative to solid phase organic synthesis (SPOS).[15] We now report the synthesis of glutamic acid analogues via a Heck reaction with a high regio- and stereoselectivity around the trisubstituted olefin.

2. Results

Substrates **3** and **4** were synthesized as described earlier[13b] by alkylation of glycine Schiff bases **1** and **2** (resp.) with methyl 2-bromomethacrylate in the presence of Cs_2CO_3 in refluxing acetonitrile (Scheme 2). **3** and **4** (1 equiv. of alkene) were submitted to the classical Heck reaction conditions, in the presence of phenyl iodide (1.1 equiv.), a catalytic amount of $Pd(OAc)_2$ (0.05 equiv.) and PPh_3 (0.1 equiv.) in the presence of an inorganic base (2.5 equiv.) in acetonitrile and in the presence or not of a phase-transfer catalyst (Scheme 2).[16] The influence of the polymer and of the base were studied in detail. Results are shown in Table 1.

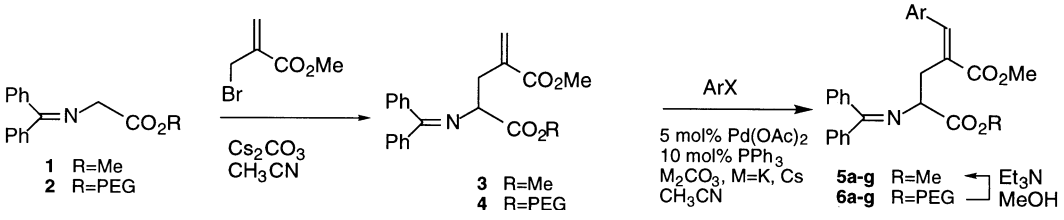
When **3** was reacted with phenyl iodide in the presence of K_2CO_3 in refluxing acetonitrile (entry 1), the reaction resulted in an incomplete conversion after 8 h. When the same reaction was carried out in the presence of a phase-transfer catalyst (entry 2) (Jeffery's conditions),[17] conversion was complete in the same amount of time and **5a** was obtained in 89% yield. PEG-supported substrate did not require a phase-transfer catalyst and the expected product **6a** was obtained in a 92% yield after 8 h (entry 4). The influence of PEG was confirmed to a certain extent by performing the Heck reaction with **3** in the presence of an external PEG catalyst (PEG 3400-OMe) (entry 3). Nevertheless, in this case, conversion was inferior to the one obtained with the supported starting material.

^1H, ^{13}C and NOESY 2D NMR confirmed the obtention of **5a** (resp. **6a**) as only one regio- and stereoisomer around the double bond.

We have already shown that in the PEG-supported alkylation of glycine ester the nature of the base can accelerate the reaction.[13b] We investigated the possibility of replacing K_2CO_3 by Cs_2CO_3 in this Heck reaction. The reaction was then faster and completion was obtained in 2 h (entry 5). Yields were comparable. Since reaction time was dramatically reduced, we considered running the reaction at room temperature instead of refluxing acetonitrile. In the same conditions except for the temperature (entry 6) the reaction was complete in 24 h.

To explore the scope of this reaction, we considered various types of electrophiles (Table 2). Reactions were performed on PEG-supported starting material **4** since this would ease the process of purification especially in the parallel synthesis mode. In each case the product was obtained as one compound with the stereo- and regiochemistry described earlier. Aryl iodides as well as aryl bromides could be used but aryl chorides reacted too slowly to be of practical use. Electron donating groups as well as electron withdrawing groups could be borne on the electrophile. When electron withdrawing groups were present on the electrophiles, the reaction was slower and completed within 14 h when K_2CO_3 was employed as a base.

Finally since alkylation and Heck reaction conditions were similar (both using Cs_2CO_3 in refluxing acetonitrile) both of these reactions were ran in one flask. The reaction sequence was carried out in one-pot by mixing directly all the components involved. We tested this sequence of reactions in the synthesis of compound **5a**. **2** was mixed with 1.5 equiv. per methylene function of methyl 2-bromomethylacrylate in



Scheme 2. PEG–OH=HO–$(CH_2CH_2O)_n$–H with an average molecular weight of 3400.

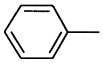
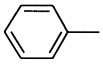
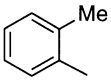
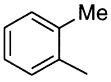
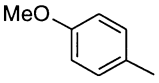
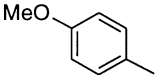
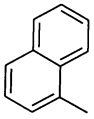
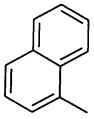
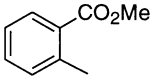
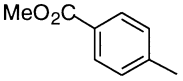
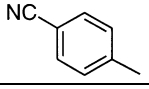
Table 1. Reaction conditions for the Heck reaction

Entry	Base	Starting material	Additive	T (°C)	t (h)	Conversion (%)	Yield of **5a** or **6a** (%)
1	K_2CO_3	**3**	–	Reflux	8	51	–[a]
2	K_2CO_3	**3**	n-Bu_4NBr	Reflux	8	100	73
3	K_2CO_3	**3**	PEG 3400-OMe	Reflux	8	78	83
4	K_2CO_3	**4**	–	Reflux	8	100	92
5	Cs_2CO_3	**4**	–	Reflux	2	100	89
6	Cs_2CO_3	**4**	–	rt	24	100	82

Experimental conditions: 1 equiv. of substituted methyl methacrylate, 1.1 equiv. of PhI, 0.1 equiv. of PPh_3, 0.05 equiv. of $Pd(OAc)_2$, 2.5 equiv. of M_2CO_3 in CH_3CN.

[a] Not determined.

Table 2. Synthesis of glutamic acid analogues

6	Ar-	X	Base	Reaction time (h)	Yield of **6** (%)	Yield of **5**[a] (%)
a		I	K_2CO_3	8	92	80
a		I	Cs_2CO_3	2	89	–[b]
b		I	K_2CO_3	8	93	80
b		I	Cs_2CO_3	2	72	–[b]
c		I	K_2CO_3	8	88	79
c		I	Cs_2CO_3	2	77	–[b]
d		Br	K_2CO_3	14	86	92
d		Br	Cs_2CO_3	4	95	–[b]
e		I	K_2CO_3	14	95	77
f		Br	K_2CO_3	24	72	71
g		Br	K_2CO_3	24	75	67

Experimental conditions: 1 equiv. of substituted methacrylate, 1.1 equiv. ArX, 0.1 equiv. of PPh_3, 0.05 equiv. of $Pd(OAc)_2$, 2.5 equiv. of M_2CO_3 in refluxing CH_3CN.

[a] **5a–g** were obtained by transesterification of **6** by Et_3N in MeOH.

[b] Not performed.

the presence of 2 equiv. of Cs_2CO_3, PhI (1.75 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and PPh_3 (0.1 equiv.). After 6 h, **5a** was obtained as the sole product in 85% yield. It has to be noted that this yield is slightly higher than the overall yield obtained when the reactions were run sequentially.

Cleavage from the PEG was performed by transesterification with MeOH in the presence of triethylamine to yield the corresponding methyl ester.[13b]

3. Discussion

3.1. Heck reaction

As pointed out in Table 1 we can notice that the presence of a soluble PEG polymer has a positive influence on the reaction kinetics. As it has been shown by us[13d] and others[18] in the Heck reaction a soluble polymeric support may act as solvent. A substrate or a reactant when present in a polymeric environment may react differently at least from a kinetic point of view. One explanation in the case of the Heck reaction could be that the PEG is acting as a phase-tranfer agent, chelating strongly the cation of the inorganic base and transferring the anion in the organic solvent, in way similar to the one of a crown ether[19] and is usually obtained with the more commonly employed quaternary ammonium salt.[17] Nevertheless we cannot exclude also the possibility for the polymer to influence the stability of the reactive intermediates involved in the catalytic cycle through participation of the polymeric oxygens.

The catalytic system which was used ($Pd(OAc)_2$, PPh_3) with K_2CO_3 or Cs_2CO_3 as base was very efficient for coupling a

1,1-disubstituted olefin with both electron rich and electron poor arenes even in the case of an *ortho* substitution. In all cases, no second Heck arylation (which is often a side reaction) occurred. In each case essentially complete control of regio- and stereoselectivity was obtained. In the literature, it was reported several times that a Heck reaction performed on a α-substituted α,β-unsaturated esters yields a mixture of isomers.[2–9] Usually the major isomer is the 'classical' Heck reaction product with the aryl group in the *trans* position to the ester function. The isomer distribution seems both to depend on the nature of the catalytic system and on the nature of the second substituent of the starting alkene. It is generally admitted that in a Heck reaction regio- and stereoselectivity ratios are determined at the β-elimination step which is ruled by the Curtin–Hammett control principle reflecting the energy of the respective transition states.[1e] Nevertheless, isomerization of the products often occurs after initial β-elimination is achieved. In the present system, as it has been pointed out before, the source of selectivity for this type of substrate seems to be thermodynamic in nature[8] but it seems unlikely that the selectivity is due only to the difference in steric effects generated by the ester group or the substituent.[4]

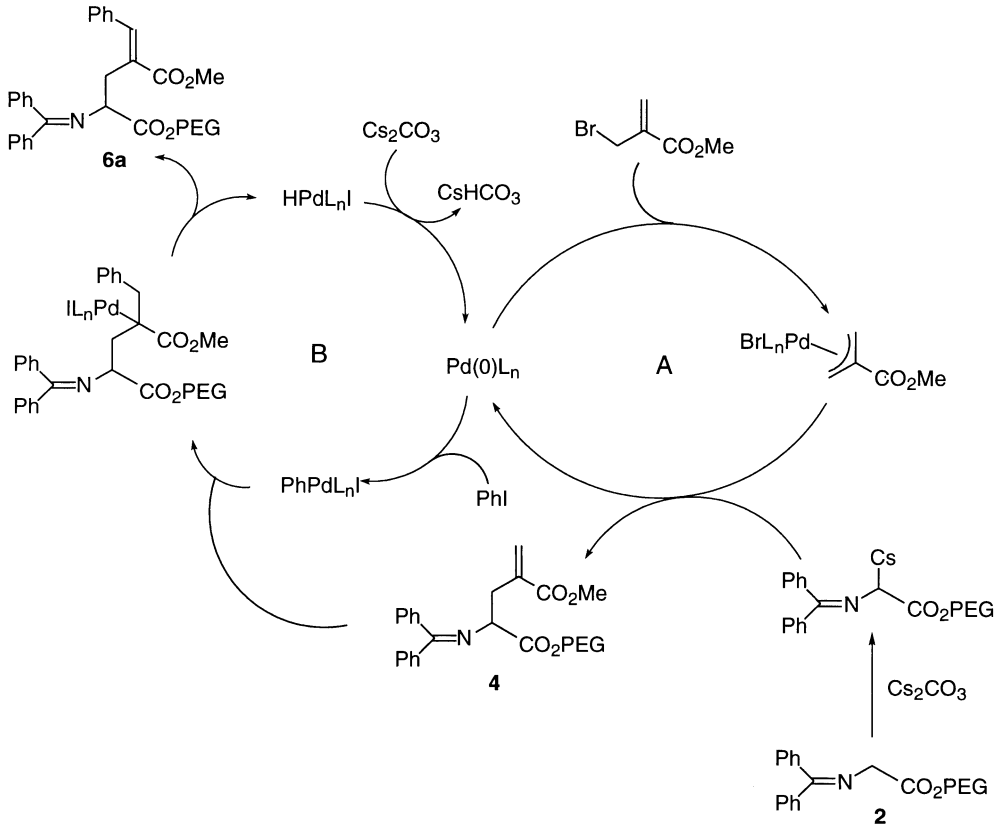
In the case of butyl methacrylate, best selectivities were obtained with a palladacycle[7] or a pincer complex.[9] It appeared that for a given catalyst the nature of the base (inorganic vs organic) is significant. Good regio- and *E*/*Z*-selectivities could be obtained with both organic and inorganic bases depending on the catalytic system. This may reflect the structure of the various palladium complexes formed in the presence of one or the other base but also that isomerization can be more efficient depending on the base.

In the case of a heteroatom substitution at the α-carbon, in almost every case the *Z*-isomer was obtained (which correspond still to a *trans* position of the entering aryl group to the ester).[2,5,6]

Examples of arylation of 2-substituted methacrylate are scarce in the literature[4,8] and they have a tendency to yield a mixture of compounds. In the case presented herein the α-substituted α,β-unsaturated ester is prone to yield a high stereoselectivity in spite of the use of a classical Heck reaction system.

3.2. One-pot alkylation/Heck reaction

From what is known about the mechanism of the Heck reaction[1] and the Pd-catalyzed allylation,[20] the following mechanism for the one-pot Heck reaction can be written (Scheme 3). The palladium catalyst probably participates in two different catalytic cycles. In catalytic system A, reaction of Pd(0) with methyl 2-bromomethylacrylate generated a π-allyl palladium intermediate[21] which then reacts with the activated methylene enolate of **2**[22] to generate the alkylated product **4** and recycle Pd(0). In catalytic system B, Pd(0) oxidatively adds to the C–I bond of PhI. Insertion in the olefin followed by β-elimination yielded the final product **6** and the hydridopalladium complex. Reaction with the base regenerated the Pd-catalyst. One cannot rule out a mechanism in which the Heck reaction would occur



Scheme 3.

directly on methyl 2-bromomethylacrylate. A control experiment was carried out: methyl 2-bromomethylacrylate was reacted with PhI in the Heck reaction conditions. This did not yield the substituted olefin but rather a complex mixture. Pd-catalyzed cascade reactions have been extensively studied[10] but to our knowledge few examples of combination of Pd-catalyzed allylation and Heck reaction of the subsequent olefin exist in the literature.[23] In the case we are reporting, the one-pot reaction generates simultaneously two C–C bonds to produce a regio- and a stereodefined trisusbstituted olefin. Further investigation to delineate the scope of this reaction is under study in our laboratory.

4. Experimental

4.1. General

All reagents including PEG 3400 were obtained from Aldrich Chemical Co. and used without purification. ^{1}H and ^{13}C NMR analyses were performed with a Brüker Advance DPX-200 and 400 MHz, respectively. Mass spectra (electrospray ionization mode ESIMS) were taken on a Platform II (Micromass, Manchester, UK) quadrupole mass spectrometer fitted with an electrospray interface.

4.1.1. Methyl (2-*N*-(diphenylmethylene amino)-5-phenyl-4-methoxycarbonyl-4-(*E*)-pentenoate) (5a). A mixture of **3** (0.088 g, 0.25 mmol), phenyl iodide (0.056 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and inorganic base (0.625 mmol) in 10 ml of CH_3CN was refluxed for the indicated time. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, and filtered. Then, in the case of PEG-OMe used as catalyst, the solution was precipitated in Et_2O and the filtrate was dried in vacuo. When *n*-Bu_4NBr was used as catalyst, the CH_2Cl_2 solution was filtered and the filtrate was washed three times with water, dried on $MgSO_4$, concentrated, and dried in vacuo.

(a) With K_2CO_3 (0.09 g, 0.625 mmol): the reaction mixture was refluxed for 26 h to yield 0.085 g (80%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.00 (dd, J=13.5, 8.5 Hz, 1H), 3.20 (dd, J=3.2, 13.5 Hz, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 4.50 (dd, J=3.2, 10.4 Hz, 1H), 6.65–7.80 (m, 15H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 32.52, 51.86, 61.81, 64.33, 69.35, 70.14–71.18, 72.71, 128.19, 128.44, 128.59, 128.68, 128.77, 128.83, 128.94, 129.15, 129.39, 130.11, 130.54, 130.79, 132.14, 132.35, 132.71, 135.16, 136.47, 139.89, 142.54, 169.38, 171.85, 172.13; MS (electrospray) m/e=428.56 (M+1).

(b) With K_2CO_3 (0.09 g, 0.625 mmol) and PEG 3400-OMe (0.43 g, 0.125 mmol): the reaction mixture was refluxed for 14 h to yield 0.089 g (83%) of the title compound.

(c) With K_2CO_3 (0.09 g, 0.625 mmol) and *n*-Bu_4NBr (0.081 g, 0.25 mmol): the reaction mixture was refluxed for 8 h to yield 0.078 g (73%) of the title compound.

(d) With Cs_2CO_3 (0.20 g, 0.625 mmol): the reaction mixture was refluxed for 6 h to yield 0.084 g (79%) of the title compound.

4.1.2. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-phenyl-4-methoxycarbonyl-4-(*E*) pentenoate) (6a). A mixture of **4** (0.505 g, 0.125 mmol), phenyl iodide (0.06 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and inorganic base (0.625 mmol) in 10 ml of CH_3CN was refluxed for the indicated time. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo.

(a) With K_2CO_3 (0.086 g, 0.625 mmol): the reaction mixture was refluxed for 8 h to yield 0.48 g (92%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.70 (s large, 150H), 3.80 (s, 3H), 4.50 (dd, J=3.5, 10.4 Hz, 1H), 7.20–7.80 (m, 15H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 31.22, 52.15, 61.48, 64.38, 64.65, 69.35, 70.06–70.99, 72.78, 128.29, 128.54, 128.68, 128.72, 128.80, 128.85, 128.91, 129.05, 129.33, 130.21, 130.46, 130.71, 132.36, 132.44, 132.53, 132.83, 135.52, 136.27, 139.47, 142.77, 168.48, 171.54, 171.98.

(b) With Cs_2CO_3 (0.20 g, 0.625 mmol): the reaction mixture was refluxed for 2 h to yield 0.47 g (89%) of the title compound.

(c) With Cs_2CO_3 (0.20 g, 0.625 mmol): the reaction mixture was stirred at room temperature for 24 h to yield 0.43 g (82%) of the title compound.

4.1.3. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-*o*-tolyl-4-methoxycarbonyl-4-(*E*)-pentenoate) (6b). A mixture of **4** (0.505 g, 0.125 mmol), 2-iodotoluene (0.06 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and inorganic base (0.625 mmol) in 10 ml of CH_3CN was refluxed for the indicated time. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo.

(a) With K_2CO_3 (0.086 g, 0.625 mmol): the reaction mixture was refluxed for 8 h to yield 0.49 g (93%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.10 (s, 3H), 3.00 (dd, J=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.70 (s large, 150H), 4.15–4.25 (m, 2H), 4.45 (dd, J=3.2, 10.4 Hz, 1H), 7.10–7.60 (m, 14H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 18.82, 28.63, 50.87, 64.25, 67.41, 70.14–71.45, 72.56, 127.42, 127.81, 128.55, 128.73, 129.00, 129.29, 130.95, 131.06, 131.58, 133.89, 134.97, 138.34, 140.13, 166.87, 169.14, 171.07, 171.95.

(b) With Cs_2CO_3 (0.24 g, 0.75 mmol): the reaction mixture was refluxed for 2 h to yield 0.38 g (72%) of the title compound.

4.1.4. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-(*p*-anisyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (6c). A mixture of **4** (0.505 g, 0.125 mmol),

4-iodoanisole (0.07 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and inorganic base (0.625 mmol) in 10 ml of CH_3CN was refluxed for the indicated time. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo.

(a) With K_2CO_3 (0.086 g, 0.625 mmol): the reaction mixture was refluxed for 8 h to yield 0.47 g (88%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.00 (dd, J=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.80 (s large, 150H), 3.90 (s, 3H), 4.20–4.35 (m, 2H), 4.50 (dd, J=3.5, 10.5 Hz, 1H), 6.95–7.80 (m, 14H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 31.19, 52.12, 56.73, 64.57, 69.33, 70.38–70.89, 72.34, 114.20, 116.68, 116.83, 128.25, 128.46, 128.69, 128.76, 129.25, 130.14, 130.68, 132.09, 136.37, 136.49, 139.47, 142.66, 165.20, 168.39, 171.47, 171.95.

(b) With Cs_2CO_3 (0.20 g, 0.625 mmol): the reaction mixture was refluxed for 2 h to yield 0.41 g (77%) of the title compound.

4.1.5. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-(α-naphthyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (6d). A mixture of **4** (0.505 g, 0.125 mmol), α-naphthyl bromide (0.06 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and inorganic base (0.625 mmol) in 10 ml of CH_3CN was refluxed for the indicated time. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo.

(a) With K_2CO_3 (0.086 g, 0.625 mmol): the reaction mixture was refluxed for 14 h to yield 0.47 g (86%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.00 (dd, J=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.80 (s large, 150H), 4.20–4.40 (m, 2H), 4.50 (dd, J=3.5, 10.5 Hz, 1H), 7.15–7.90 (m, 17H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.12, 52.23, 61.74, 64.42, 66.28, 69.27, 70.32–70.90, 72.92, 126.45, 126.70, 127.58, 128.27, 128.31, 128.53, 128.57, 128.74, 128.79, 128.82, 128.87, 128.91, 128.95, 129.27, 129.35, 130.24, 130.65, 133.81, 139.44, 141.18, 168.26, 171.38, 171.83.

(b) With Cs_2CO_3 (0.20 g, 0.625 mmol): the reaction mixture was refluxed for 4 h to yield 0.51 g (95%) of the title compound.

4.1.6. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethyleneamino)-5-(*o*-methoxycarbonyl phenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (6e). A mixture of **4** (0.505 g, 0.125 mmol), methyl-2-iodobenzoate (0.072 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and K_2CO_3 (0.086 g, 0.625 mmol) in 10 ml of CH_3CN was refluxed for 14 h. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo to yield 0.51 g (95%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.00 (dd, J=8.5, 16.0 Hz), 3.25 (dd, J=3.5, 16.0 Hz), 3.50–3.70 (s large, 150H), 3.75 (s, 3H), 4.20–4.40 (m, 2H), 4.45 (dd, J=3.5, 10.5 Hz, 1H), 7.15–7.80 (m, 14H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.71, 52.14, 60.95, 64.27, 64.50, 69.84, 70.24–70.82, 72.53, 127.52, 128.22, 128.58, 128.71, 128.81, 128.91, 129.06, 129.29, 130.41, 130.58, 131.02, 131.23, 132.75, 135.10, 136.35, 138.12, 139.44, 144.33, 161.47, 166.52, 168.13, 171.26, 171.92.

4.1.7. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-(*p*-methoxycarbonylphenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (6f). A mixture of **4** (0.505 g, 0.125 mmol), methyl-4-bromobenzoate (0.06 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and K_2CO_3 (0.086 g, 0.625 mmol) in 10 ml of CH_3CN was refluxed for 24 h. After cooling, the base and the palladium were filtered under celite and the filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo to yield 0.39 g (72%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J_1=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.70 (s large, 150H), 3.90 (s, 3H), 4.20–4.40 (m, 2H), 4.50 (dd, J=3.5, 10.5 Hz, 1H), 7.15–7.70 (m, 14H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.09, 52.14, 52.31, 52.64, 61.86, 64.39, 69.34, 70.46–70.92, 72.95, 128.29, 128.37, 128.50, 128.55, 128.72, 128.76, 128.81, 128.89, 129.05, 129.28, 129.33, 130.01, 130.05, 130.22, 135.53, 136.30, 139.49, 142.77, 168.49, 171.65, 171.72, 171.96.

4.1.8. Poly(ethylene glycol)-3400 di(2-*N*-(diphenylmethylene amino)-5-(*p*-cyanophenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (6g). A mixture of **4** (0.505 g, 0.125 mmol), 4-bromobenzonitrile (0.05 g, 0.275 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), PPh_3 (0.006 g, 0.025 mmol) and K_2CO_3 (0.086 g, 0.625 mmol) in 10 ml of CH_3CN was refluxed for 24 h. After cooling, the base and the palladium were filtered over celite. The filtrate was concentrated, dissolved in CH_2Cl_2, filtered and then precipitated in Et_2O. The product was filtered and dried in vacuo to yield 0.40 g (75%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J_1=8.5, 13.5 Hz, 1H), 3.25 (dd, J=3.5, 13.5 Hz, 1H), 3.50–3.70 (s large, 150H), 4.20–4.40 (m, 2H), 4.50 (dd, J=3.5, 10.5 Hz, 1H), 7.15–7.70 (m, 14H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.32, 53.95, 61.70, 64.69, 69.22, 70.03–71.63, 73.02, 118.52, 128.21, 128.29, 128.44, 128.63, 128.80, 128.92, 129.16, 130.35, 130.62, 132.34, 132.79, 133.42, 136.70, 139.73, 142.32, 168.45, 171.41, 171.83.

4.1.9. Cleavage of poly(ethylene glycol)-3400. A solution of poly(ethylene glycol)-3400 supported substituted Schiff base (1 equiv., 0.25 mmol) and NEt_3 (20% v/v in MeOH, 2 ml) was heated under reflux for 48 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and precipitated in ether. The PEG free was filtered, and the filtrate was washed three times with water and dried in vacuo to give the methyl ester derivative.

4.1.10. Methyl (2-*N*-(diphenylmethylene amino)-5-phenyl-4-methoxycarbonyl-4-(*E*)-pentenoate) (5a). With **6a** (1.05 g, 0.25 mmol) to yield 0.16 g (80%) of the title compound: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J=8.5,

13.5 Hz, 1H); 3.25 (dd, J=3.5, 13.5 Hz, 1H); 3.75 (s, 3H); 3.85 (s, 3H); 4.20–4.30 (m, 1H); 7.20–7.80 (m, 15H); 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 32.52, 51.86, 61.81, 64.33, 69.35, 70.14–71.18, 72.71, 128.19, 128.44, 128.59, 128.68, 128.77, 128.83, 128.94, 129.15, 129.39, 130.11, 130.54, 130.79, 132.14, 132.35, 132.71, 135.16, 136.47, 139.89, 142.54, 169.38, 171.85, 172.13. MS (electrospray) m/e=428.17 (M+1).

4.1.11. Methyl (2-*N*-(diphenylmethylene amino)-5-(*o*-tolyl)-4-methoxycarbonyl-4 (*E*)-pentenoate) (5b). With **6b** (1.05 g, 0.25 mmol) to yield 0.17 g (77%) of the title compound:^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.10 (s, 3H); 3.05 (dd, J_1=3.8, 13.5 Hz, 1H); 3.25 (dd, J_1=9.0, 13.5 Hz, 1H); 3.55 (s, 3H); 3.65 (s, 3H); 4.50 (dd, J=3.8, 9.5 Hz, 1H); 7.10–7.65 (m, 14H); 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 18.94, 28.68, 51.22, 54.30, 63.09, 69.54, 124.72, 126.87, 127.06, 127.25, 127.35, 127.40, 127.48, 127.92, 128.11, 128.98, 129.03, 129.32, 131.02, 131.12, 131.38, 133.41, 134.96, 138.11, 140.65, 166.94, 169.73, 171.07. MS (electrospray) m/e=442.14 (M+1).

4.1.12. Methyl (2-*N*-(diphenylmethylene amino)-5-(*p*-anisyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (5c). With **6c** (1.06 g, 0.25 mmol) to yield 0.18 g (79%) of the title compound. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J=3.6, 13.5 Hz, 1H); 3.25 (dd, J=7.5, 13.5 Hz, 1H); 3.55 (s, 3H); 3.75 (s, 3H); 3.85 (s, 3H); 4.55 (dd, J=3.6, 10.3 Hz, 1H); 6.90–7.70 (m, 14H); 7.75 (s, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ 28.68, 51.22, 54.30, 64.84, 69.54, 112.84, 125.19, 126.69, 126.87, 127.12, 127.28, 127.44, 127.93, 129.04, 130.71, 134.91, 138.14, 141.10, 159.04, 167.35, 170.05, 171.35. MS (electrospray) m/e=458.54 (M+1).

4.1.13. Methyl 2-*N*-(diphenylmethylene amino)-5-(α-naphtyl)-4-methoxycarbonyl-4-(*E*)-pentenoate (5d). With **6d** (1.07 g, 0.25 mmol) to yield 0.22 g (92%) of the title compound. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.05 (dd, J=4.0, 13.5 Hz, 1H); 3.25 (dd, J=8.5, 13.5 Hz, 1H); 3.65 (s, 3H); 3.80 (s, 3H); 4.55 (dd, J=4.0, 9.5 Hz, 1H); 7.10–7.90 (m, 17H); 8.25 (s, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ 28.68, 50.77, 51.10, 64.84, 67.14, 69.51, 125.00, 125.26, 126.05, 126.84, 126.95, 127.06, 127.10, 127.25, 127.36, 127.37, 127.43, 127.52, 127.54, 127.79, 127.87, 127.99, 129.04, 129.22, 131.39, 136.58, 139.78, 142.21, 167.04, 169.89, 170.48, 171.05. MS (electrospray) m/e=477.60 (M+1).

4.1.14. Methyl (2-*N*-(diphenylmethylene amino)-5-(*o*-methoxycarbonyl phenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (5e). With **6e** (1.08 g, 0.25 mmol) to yield 0.19 g (77%) of the title compound:^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.95–3.30 (m, 2H); 3.50 (s, 3H); 3.60 (s, 3H);3.75 (s, 3H); 4.45 (dd, J=3.3, 9.8 Hz, 1H); 7.15–8.10 (m, 14H); 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 31.01, 52.17, 52.29, 52.33, 64.41, 127.72, 128.26, 128.31, 128.55, 128.64, 128.75, 128.79, 129.18, 130.54, 131.08, 131.26, 131.35, 132.78, 133.07, 136.51, 138.19, 139.60, 141.74, 144.31, 166.61, 168.23, 171.27, 172.57; MS (electrospray) m/e=486.21 (M+1).

4.1.15. Methyl (2-*N*-(diphenylmethylene amino)-5-(*p*-methoxycarbonyl phenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (5f). With **6f** (1.08 g, 0.25 mmol) to yield 0.17 g (71%) of the title compound; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.90–3.15 (m, 2H); 3.55 (s, 3H); 3.70 (s, 3H); 3.90 (s, 3H); 4.55 (dd, J_1=3.8, 10.3 Hz, 1H); 7.10–7.80 (m, 14H); 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.86, 52.11, 52.20, 52.47, 64.21, 127.65, 128.31, 128.42, 128.53, 128.59, 128.72, 128.82, 129.64, 130.13, 131.01, 131.17, 131.58, 132.69, 132.98, 136.22, 138.55, 139.10, 141.87, 144.44, 166.51, 168.01, 171.13, 172.18. MS (electrospray) m/e=485.95 (M+1).

4.1.16. Methyl (2-*N*-(diphenylmethylene amino)-5-(*p*-cyanophenyl)-4-methoxycarbonyl-4-(*E*)-pentenoate) (5g). With **6g** (1.06 g, 0.25 mmol) to yield 0.15 g (67%) of the title compound:^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.00 (dd, J=3.2, 13.5 Hz, 1H); 3.30 (dd, $_1$=9.5, 13.5 Hz, 1H); 3.55 (s, 3H); 3.65 (s, 3H); 4.50 (dd, J=3.2, 10.4 Hz, 1H); 7.15–7.70 (m, 14H); 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 30.32, 53.33, 53.95, 64.98, 118.12, 128.14, 128.18, 128.33, 128.52, 128.79, 128.81, 129.05, 130.24, 130.53, 132.18, 132.89, 133.31, 136.59, 139.61, 142.41, 168.84, 171.00, 171.75; MS (electrospray) m/e=453.97 (M+1).

Acknowledgements

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