Pergamon

Tetrahedron 56 (2000) 2239–2246

TETRAHEDRON

4-Quinolylmethyl and 1-Naphthylmethyl as Benzyl-type Protecting Groups of Carboxylic Acids Removable by Homogeneous Palladium-Catalyzed Hydrogenolysis

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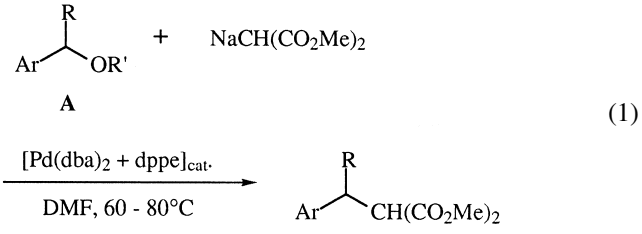
Accepted 7 December 1999

Abstract—4-Quinolylmethyl (4-QUI) esters are reduced by palladium-catalyzed hydrogenolysis by formate anion. The reaction conditions are compatible with reducible substituents or functional groups as aromatic bromo, alkene, aldehyde, ketone, nitrile, ethyl and benzyl esters. An allyl ester is cleaved selectively in the presence of a 4-QUI ester. 1-Naphthylmethyl (1-NAP) esters of α-amino acids could be deprotected without any racemization by the same methodology. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

In the recent years, we have developed a new palladium-catalyzed reaction on naphthylmethyl and 1-naphthylethyl esters. Namely substrates of type **A** undergo a palladium-catalyzed nucleophilic substitution by alkali salt of dimethylmalonate under conditions depicted in Eq. (1).[1–4]



(1)

Ar=1- or 2-naphthyl; R=H or Me; R′=COMe or CO_2Me; $Pd(dba)_2$=bis(dibenzylideneacetone)palladium(0); dppe=1,2-bis(diphenylphosphino)ethane.

The main features for this transformation are:

- the substitution reaction does not take place in the absence of a palladium source;
- chelating diphosphines are better ligands for palladium than monophosphines (i.e. PPh_3);
- substrates **A** where Ar is phenyl are inert under the reaction conditions, but give satisfactory yields of substitution products when Ar is 1- or 2-naphthyl, and more generally when Ar is a condensed aromatic;
- the reaction is ready with naphthylmethyl esters (**A**, Ar=naphthyl, R=H: 75–77% at 60°C) and more difficult with 1-naphthylethyl esters (**A**, Ar=naphthyl, R=Me: 77–79% yield at 80°C);[1]
- the reaction is regioselective to give a clean replacement of the leaving group OR′ by the nucleophile;
- the order of reactivity of substrates follows the leaving group ability: acetates are less reactive than trifluoroacetates and methyl carbonates.[1,2]

The above results suggest that the mechanism is analogous to the mechanism for the palladium-catalyzed allylic substitution (Tsuji–Trost reaction), i.e. oxidative addition to give a π-benzylic-type cationic palladium complex (with a partial loss of resonance energy) which undergoes regioselective nucleophilic attack to the non-cyclic allylic carbon terminus restoring the resonance energy. These two processes should be stereospecific, both taking place with inversion of configuration (backside displacement of the leaving group followed by a nucleophilic attack *anti* to the palladium).[2]

The reaction is stereoselective: enantiomerically pure 1-(1-naphthyl)ethyl and 1-(2-naphthyl)ethyl carbonates are substituted with high (>90%) stereoselectivity affording products with overall retention of configuration.[2]

Through the use of chiral diphosphine ligands, enantiomerically enriched products (up to 61%) were obtained from racemic 1-(1-naphthyl)ethyl and 1-(2-naphthyl)ethyl acetates by enantioselective palladium-catalyzed substitution.[3]

Stabilized carbonucleophiles are good nucleophiles.

Keywords: catalysis; palladium and compounds; protecting groups; quinolines.

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PII: S0040-4020(99)01108-4

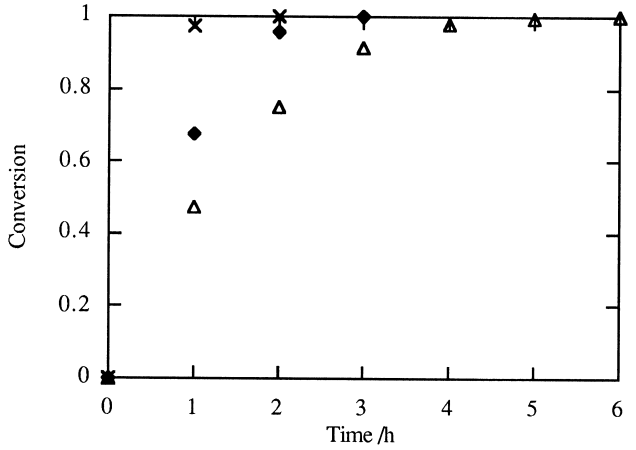
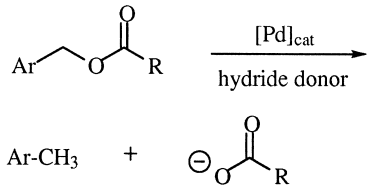


Figure 1. Conversion of NAP and QUI acetates (reaction 2, 4 equiv. ammonium formate, 2 mol% $Pd(dba)_2$, 2.5 mol% dppe, DMSO, 80°C); △: 1-NAP **1**; ◆: 3-QUI **3**; ×: 4-QUI **4**.

Secondary amines afford substitution products provided the solvent is THF or DMPU. DMF serves as a dimethylamino source yielding a convenient way to synthesize *N*,*N*-dimethyl-(1 or 2)-naphthylmethylamine from the corresponding acetate.[4]

Using hydride donors as reducing nucleophiles appears not to be useful for enantioselective synthesis. We thought however that such a reaction could be of some interest when involved in a deprotection sequence of acids protected as arylmethyl esters (Eq. (2)).



(2)

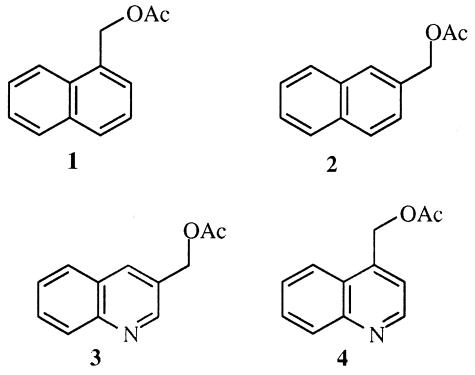
Allyl and benzyl groups are frequently used for the protection of carboxylic acids[5,6] in organic synthesis. They are removed by palladium-catalyzed allyl capture strategy[7] and palladium-catalyzed hydrogenolysis, respectively. Although the former reaction is a homogeneous catalytic process, the removal of a benzyl group is a heterogeneous one and it could be a serious drawback especially in the context of chemical synthesis on solid support. Recently, Spencer developed the 2-naphthylmethyl (2-NAP) group as a carboxylic acid protecting group that can be removed selectively in the presence of benzyl esters by preferential palladium-on-carbon-catalyzed hydrogenolysis, because of the higher binding affinity of the 2-NAP group to the metal surface.[8] However, control of the reaction conditions is probably necessary to avoid a full deprotection of a 2-NAP benzyl dissymmetric diester.

This paper reports an application of the palladium-catalyzed substitution reaction presented above to the cleavage of a benzyl-type protecting group of carboxylic acids. The deprotection was realized by homogeneous palladium-catalyzed hydrogenolysis of 4-quinolylmethyl (4-QUI) esters by ammonium formate. The tolerance of some reducible functional groups to the reaction conditions was examined. Some of the presented results were already published in a preliminary communication.[9]

Results and Discussion

Influences of the reducing agent, the solvent and the catalyst ligand were first briefly examined in the reduction of 1-naphthylmethyl (1-NAP) acetate **1**. The reactions were followed by GC. In DMF at 60°C, the decreased order of reactivity was $HCOONa \approx HCOONH_4 > HCOOH/NEt_3$ [catalyst=$Pd(dba)_2$ (2 mol%)+dppe (2.5 mol%)]. Phenylsilane which was recently used as an allyl scavenger[10] was totally ineffective in this reaction. Using ammonium formate with the same catalyst at 60°C, the reaction was faster in DMSO (about 80% conversion of **1** in 24 h) than in DMF or THF (about 50 and 10% conversion, respectively, in 48 h).

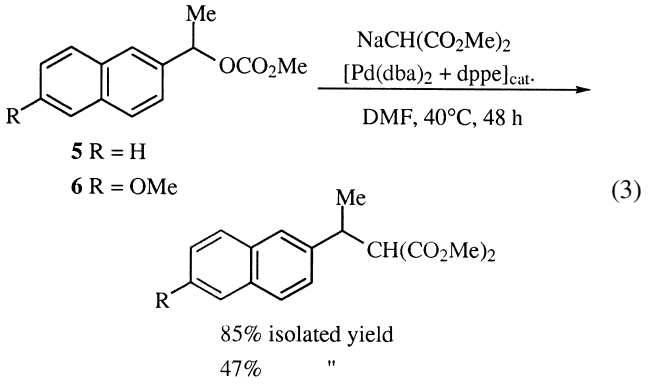
The reaction of **1** (4 equiv. ammonium formate, DMF, 60°C) afforded the reduction product in 50% yield in 48 h with 2 mol% $Pd(dba)_2$ and 2.5 mol% dppe as a ligand, whereas 6 days were required to reach this yield when using 4.5 mol% of either PPh_3 or $P(n\text{Bu})_3$ as a ligand under the same conditions. These results are in agreement with our previous findings that dppe was more efficient than PPh_3 as ligand in the palladium-catalyzed substitution of **1** by sodium dimethylmalonate.[2]



1- and 2-NAP acetates **1** and **2** underwent palladium-catalyzed substitution by dimethylmalonate anion in THF at 60°C in 24 h. In the same conditions, we have observed a more rapid reaction on 3- and 4-QUI acetates **3** and **4**,[11] which were prepared from the corresponding quinolinecarboxaldehydes by $NaBH_4$ reduction followed by acetylation (Ac_2O, Et_3N, catalytic DMAP in diethyl ether). We first compared the reactivity of **1**–**4** in the palladium-catalyzed reduction by ammonium formate in DMSO at 80°C. For this purpose, the reaction was monitored by ^1H NMR using 1,3,5-trimethoxybenzene as an internal reference. The conversion of the starting acetate was evaluated by the integration of the methylene protons Ar–$\mathbf{CH_2}$–OAc (δ ca 5.3 ppm) relative to the integration of the aromatic protons of the reference (δ=6.1 ppm). Results are presented in Fig. 1.

1-NAP acetate **1** was completely consumed in 6 h and the reactivity of its 2-isomer **2** was comparable (data not shown). The heterocycles **3** and **4** were more reactive, 4-QUI acetate **4** giving the faster reaction, since the conversion was complete after 2 h (after 5 and 12 h at 60 and 40°C, respectively). These data suggested an electronic effect: the electron-withdrawing heteroaromatic in **3** or **4** was beneficial, probably for the oxidative addition step (see below).

We have already observed such an electronic effect in the substitution of carbonates **5** and **6** by sodium dimethylmalonate (Eq. (3)). The electron-donating methoxy substituent decreased the reactivity of the substrate **6** compared to the unsubstituted analogue **5**.[2]

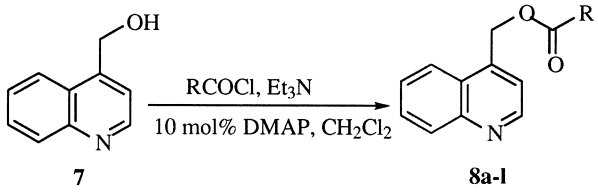


(3)

The proposed mechanism of this reaction is presented in Scheme 1. Oxidative addition of the 4-QUI acetate **4** to a palladium(0) complex generated from $Pd(dba)_2$ and dppe afforded a η^3-benzyl cationic palladium(II) intermediate **B**. This step could be regarded as an interaction between an electron-rich palladium(0) complex and the substrate. For this reason, it is favoured for a QUI substrate bearing an electron-deficient aromatic system compared to a NAP substrate.

The η^3-benzyl complex **B** may be in equilibrium with the η^1-benzyl species **C** and the latter could coordinate an hydride ligand generated by decarboxylation of ammonium formate. The neutral hydrid complex **D** undergoes a reductive elimination leading to 4-methylquinoline and closing the catalytic cycle.

We next studied the reduction of 4-QUI esters **8** containing various functional groups. Compounds **8a–l** were prepared in good yield (85–98%) by classical acylation of 4-quinolylmethanol **7** (Eq. (4)).

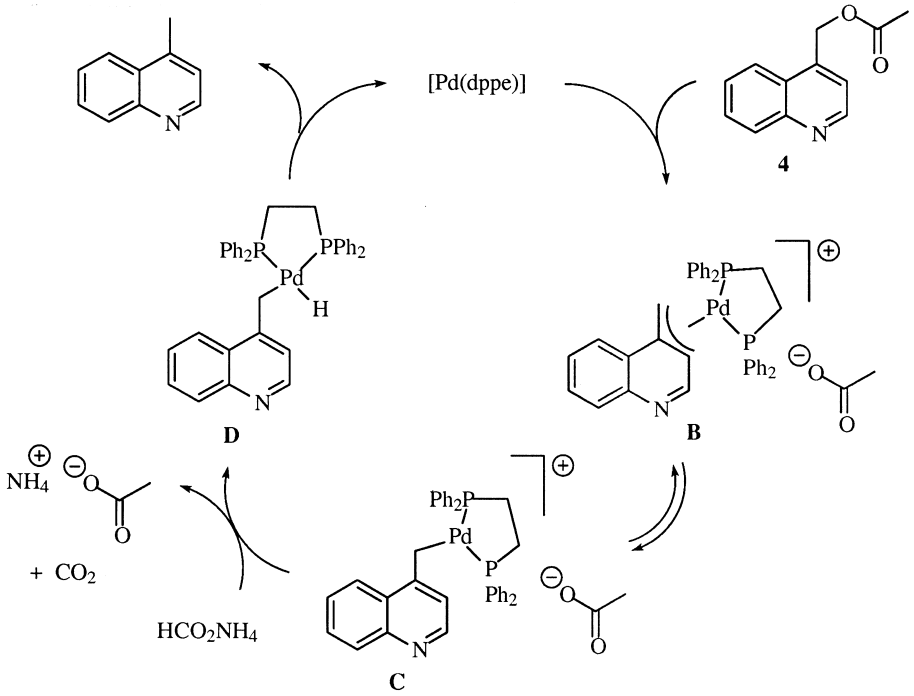


7 **8a-l**

8a	$R = (CH_2)_{10}CH_3$	**8g**	$R = C_6H_4$-pCHO
8b	$R = (CH_2)_{14}CH_3$	**8h**	$R = C_6H_4$-pNO_2
8c	$R = (CH_2)_8CH{=}CH_2$	**8i**	$R = CH_2OC_6H_5$
8d	$R = C_6H_5$	**8j**	$R = (CH_2)_4Cl$
8e	$R = C_6H_4$-pCN	**8k**	$R = (CH_2)_5COCH_3$
8f	$R = C_6H_4$-pBr	**8l**	$R = (CH_2)_2CO_2CH_2CH_3$

(4)

Dissymmetric diesters **8m** and **8n** were prepared in excellent yields by dropwise addition of one equivalent of



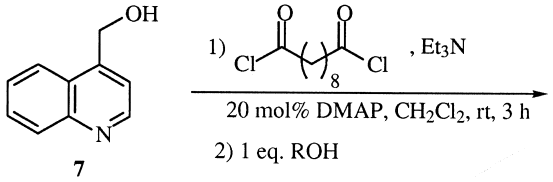
Scheme 1. Mechanism of the palladium-catalyzed reduction of 4-QUI acetate **4** by ammonium formate.

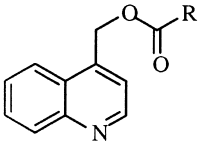
Table 1. Deprotection of 4-QUI esters **8**

Entry	Substrate	R	Product	Isolated yield (%)
1	**8a**	$(CH_2)_{10}CH_3$	**9a**	85
2	**8b**	$(CH_2)_{14}CH_3$	**9b**	90
3	**8c**	$(CH_2)_8CH{=}CH_2$	**9c**	95
4	**8d**	C_6H_5	**9d**	80
5	**8e**	C_6H_4-*p*CN	**9e**	94
6	**8f**	C_6H_4-*p*Br	**9d**	95
7[a]	**8f**	C_6H_4-*p*Br	**9f**	97
8	**8g**	C_6H_4-*p*CHO	**9g**	96
9	**8i**	$CH_2OC_6H_5$	**9i**	80
10	**8k**	$(CH_2)_5COCH_3$	**9k**	92
11	**8l**	$(CH_2)_2CO_2CH_2CH_3$	**9l**	88
12	**8m**	$(CH_2)_8CO_2CH_2C_6H_5$	**9m**	95
13	**8n**	$(CH_2)_8CO_2CH_2CH{=}CH_2$	**10**	92
14[a]	**8n**	$(CH_2)_8CO_2CH_2CH{=}CH_2$	**11**	95
15[b]	**8n**	$(CH_2)_8CO_2CH_2CH{=}CH_2$	**11**	96
16[c]	**8o**		**10**	95

[a] 1.2 equiv. HCO_2NH_4.
[b] Cat=$(Pd(PPh_3)_4$, 20°C.
[c] 8 equiv. HCO_2NH_4.

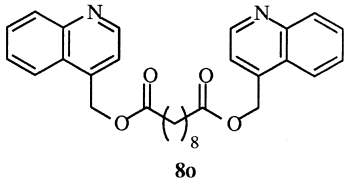
sebacoyle chloride to a solution of 4-quinolylmethanol, triethylamine and catalytic DMAP, followed by the treatment of the resulting mixture by one equivalent of benzyl or allyl alcohol, respectively (Eq. (5)). None of the symmetric diesters of sebacic acid, dibenzyl, diallyl or di(4-QUI) **8o** were produced using this reaction protocol. Finally, di(4-QUI) sebacate **8o** was efficiently prepared (85% yield) using one half equivalent of sebacoyl chloride relative to **7**.





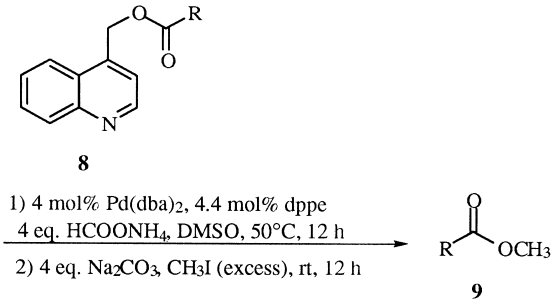
8m-n (5)

8m R = $(CH_2)_8CO_2CH_2C_6H_5$ (85%)
8n R = $(CH_2)_8CO_2CH_2CH{=}CH_2$ (90%)



8o

Deprotection reactions were conducted in DMSO at 50°C during 12 h (Eq. (6)). The carboxylic acid was isolated as its methyl ester after cleavage to facilitate the isolation, purification and identification of the product. Results are collected in Table 1.



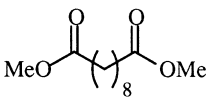
(6)

Methyl esters **9** are obtained from 4-QUI esters **8** in 80–97% yield by this deprotection/methylation sequence. The deprotection step does not affect several reducible substituents or functional groups such as alkene (entry 3), nitrile (entry 5), aldehyde (entry 8), ketone (entry 10), ethyl (entry 11) and benzyl (entry 12) esters. The total selectivity of the reaction in the case of **8m** (entry 12) is remarkable since the substrate is a dissymmetric bis benzylic diester. So we obtained here a similar result to Spencer,[8] but for a different reason. Moreover, since the oxidative addition is not observed on a benzyl substrate, control of the reaction conditions is not required to prevent the cleavage of the benzyl group.

Even an aromatic bromo substituent is compatible with the reaction conditions, provided that ammonium formate is used only in slight excess (entry 7); in the presence of four equivalents of formate, the hydrogenolysis of the carbon-bromide bond is observed (entry 6). Double deprotection of **8o** to give dimethylester **10** was accomplished in 97.5% yield for each step (entry 16).

Cleavage of both allyl and 4-quinolylmethyl groups of compound **8n** was observed in the standard reaction conditions (entry 13). No reaction took place at 30–40°C, probably by formation of complex **12a** (R,R=$(CH_2)_2$), since the oxidative addition is easier on the allyl group (see below). The catalytic cycle is stopped at this stage because of the inability of formate anion to displace the bidentate diphosphine ligand at this temperature.[12]

As expected, allyl ester of **8n** was selectively cleaved at 50°C in the presence of only a slight excess of formate (entry 14), or at room temperature with tetrakis(triphenylphosphine)palladium(0) as catalyst (entry 15) to give compound **11**. Formation of **12b** (R=Ph) is followed by monophosphine/formate exchange,[12] decarboxylation and reductive elimination on a palladium hydride species producing propene and closing the catalytic cycle.



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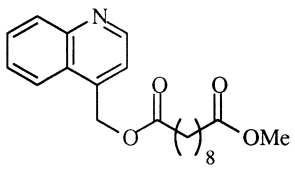
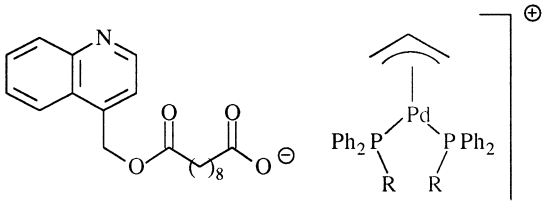


11



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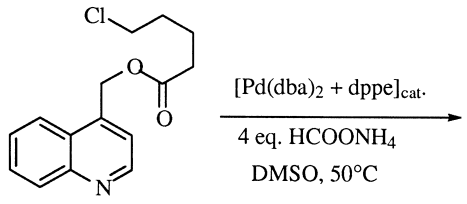
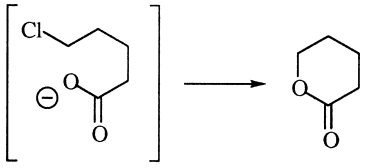
Among the substrates tested, the only limitations we have observed were:

(i) the (expected) formation of δ-valerolactone **13** from 4-QUI 5-chlorovalerate **8j** (Eq. (7));



8j (7)



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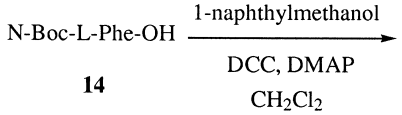
(ii) the non-selective reaction of the nitro-substituted substrate **8h** which gave an unseparable mixture of products resulting from competitive cleavage of the ester and reduction of the nitro group: characteristic signals of a para-substituted aniline were detected by analysis of the ^{1}H NMR spectrum of the mixture.

Finally, we attempted to extend this methodology to the protection of the carboxyl group of α-amino acids, but preparation of 4-QUI ester of *N*-BOC-L-phenylalanine **14** by classical coupling failed. In this case, we used 1-naphthylmethanol in the protection step and the 1-NAP ester **15** was treated in the same conditions as compounds **8** (Eq. (8)). Methyl ester **16** was obtained in 85% yield.



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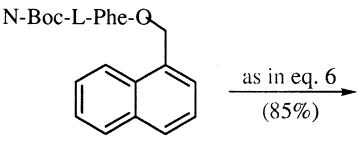

15 (8)

N-Boc-L-Phe-OMe

16

$[\alpha]_D^{20}$ - 3 (c=1, MeOH)

Comparison of the optical rotation of **16** with an authentical sample prepared from **14** indicated a complete conservation of the stereochemistry in the deprotection/methylation sequence.

Conclusion

Carboxylic acids are efficiently obtained by reductive cleavage of their 4-QUI esters promoted by formate anion. This deprotection reaction is catalyzed by a homogeneous palladium complex and is compatible with various reducible functional groups: alkene, aldehyde, ketone, ester, nitrile, aromatic bromide. Even a benzyl group survived despite its structural similarity to the 4-QUI one. Selective deprotection of allyl ester is possible in the presence of a 4-QUI ester. Although 4-methylquinoline, the product of the reductive cleavage, is not volatile (in contrast to propene resulting from the same cleavage of the allyl group), it could be easily removed from the reaction mixture by simple acidic extraction. Moreover, it allows a simple detection by thin layer chromatography. In the case of α-amino acids, the 1-NAP group is more convenient in the esterification step.

Preliminary results indicate that protected alcohols and amines as 1-NAP carbonates and carbamates, respectively, can be similarly cleaved through homogeneous palladium-catalyzed hydrogenolysis by ammonium formate. Work is actually in progress and will be reported in due course.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Coupling constants are reported in Hz. Infrared spectra were acquired using a Perkin–Elmer 883 spectrometer, and are reported in cm^{-1}. Optical rotations were measured at 20°C on a Perkin–Elmer 241 polarimeter.

All reactions involving palladium catalysis were carried out under argon using Schlenk techniques under an argon atmosphere. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone under nitrogen. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were dried over CaH_2 and distilled prior to use.

$Pd(dba)_2$ (dba denotes dibenzylideneacetone) was prepared according to a reported procedure.[13] NAP acetates **1** and **2** were prepared by acetylation (Ac_2O, Et_3N, catalytic DMAP in diethyl ether) of the corresponding commercially available alcohol. The following materials were obtained from commercial sources: 3- and 4-quinolinecarboxaldehydes; 1,3,5-trimethoxybenzene; all the acyl chlorides used in the synthesis of compounds **8** (excepted 4-formylbenzoyl chloride, prepared (oxalyl chloride, catalytic DMF in CH_2Cl_2)[14] from the corresponding commercially available acid); *N*-BOC-L-phenylalanine **14**.

Preparation of QUI acetates 3 and 4

To an ethanol (20 ml) solution of 4-quinolinecarboxaldehyde (1.58 g, 10 mmol) was added by small portions 0.45 g (12 mmol) of $NaBH_4$. After the end of the addition, the reaction mixture was stirred for 1 h at room temperature, diluted with 50 ml diethyl ether and washed with 2×50 ml of water. The aqueous phases were extracted with diethyl ether (2×20 ml) and the combined ethereal phases were dried ($MgSO_4$) and concentrated to give 1.57 g (9.9 mmol, 99% yield) of 4-quinolylmethanol **7**.[15]

4-Quinolylmethanol **7** (1.57 g, 9.9 mmol), DMAP (126 mg, 1 mmol), Et_3N (1.95 ml, 14 mmol) were dissolved in 40 ml of diethyl ether and acetic anhydride (1.15 ml, 12 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight, washed with 2×30 ml of saturated $NaHCO_3$. The organic phase was dried and concentrated. The crude product was purified by Kügelrohr distillation to give 1.54 g (7.7 mmol, 77% yield for the two steps) of 4-quinolylmethyl ethanoate **4**.[16]

Following the same procedure, 3-quinolylmethyl ethanoate **3** (1.41 g, 7.0 mmol) was obtained from 3-quinolinecarboxaldehyde (1.16 g, 7.4 mmol).

3-Quinolylmethyl ethanoate 3. Yield: 95%. ^{1}H NMR 2.07 (3H, s), 5.23 (2H, s), 7.45–7.55 (1H, m), 7.60–7.70 (1H, m), 7.77 (1H, dd, J=8 and 1.5 Hz), 8.00–8.10 (2H, m), 8.86 (1H, d, J=2 Hz). ^{13}C NMR 20.8, 63.8, 126.9, 127.5, 127.8, 128.6, 129.1, 129.8, 135.6, 147.6, 150.5, 170.6. IR 1740. HRMS calculated for $C_{12}H_{11}NO_2$: 201.0790. Found: 201.0798.

Preparation of 4-QUI esters 8a–l

A typical procedure is as follows: to a CH_2Cl_2 (5 ml) solution of 4-quinolylmethanol **7** (159 mg, 1 mmol), DMAP (12 mg, 0.1 mmol) and Et_3N (170 μl, 1.2 mmol), acyl chloride (1.1 mmol) was added dropwise. After stirring at room temperature during 24 h, the reaction mixture was diluted with 30 ml of diethyl ether and washed with 2×30 ml water. The aqueous phases were extracted with 2×20 ml of diethyl ether and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 6:4).

4-Quinolylmethyl dodecanoate 8a. Yield: 98%. ^{1}H NMR 0.80 (3H, t, J=6 Hz), 1.00–1.40 (16H, m), 1.50–1.75 (2H, m), 2.34 (2H, t, J=7.5 Hz), 5.51 (2H, s), 7.38 (1H, d, J=4.5 Hz), 7.50 (1H, t, J=7.5 Hz), 7.65 (1H, t, J=7 Hz), 7.85 (1H, d, J=8 Hz), 8.12 (1H, d, J=8.5 Hz), 8.86 (1H, d, J=4.5 Hz). ^{13}C NMR 14.1, 22.6, 24.9, 29.0–29.6 (6C), 31.8, 34.1, 62.3, 119.6, 122.9, 125.9, 127.1, 129.7, 129.8, 141.8, 147.5, 149.8, 173.3. IR 1735. HRMS calculated for $C_{22}H_{31}NO_2$: 341.2355. Found: 341.2347.

4-Quinolylmethyl hexadecanoate 8b. Yield: 85%. ^{1}H NMR 0.85 (3H, t, J=6.5 Hz), 1.05–1.45 (26H, m), 1.55–1.75 (2H, m), 2.41 (2H, t, J=7.5 Hz), 5.58 (2H, s), 7.44 (1H, d, J=4.5 Hz), 7.59 (1H, t, J=7.5 Hz), 7.73 (1H, t, J=7.5 Hz), 7.93 (1H, d, J=8.5 Hz), 8.15 (1H, d, J=8.5 Hz), 8.90 (1H, d, J=4.5 Hz). ^{13}C NMR 14.1, 22.7, 24.9, 29.1, 29.2, 29.3, 29.4, 29.5-29.7 (6C), 31.9, 34.2, 66.5, 119.7, 123.0, 126.0, 127.1, 129.6, 130.0, 141.4, 147.9, 150.1, 173.4. IR 1735. $C_{26}H_{39}NO_2$ calculated: C 78.54, H 9.89, N 3.52. Found: C 78.57, H 9.92, N 3.53.

4-Quinolylmethyl undec-10-enoate 8c. Yield: 97%. ^{1}H NMR 1.15–1.45 (10H, m), 1.63 (2H, quintet, J=6.5 Hz), 1.98 (2H, q, J=6.5 Hz), 2.39 (2H, t, J=7.5 Hz), 4.89 (1H, dd, J=10.5 and 15 Hz), 4.94 (1H, dd, J=17 and 15 Hz), 5.55 (2H, s), 5.76 (1H, ddt, J=17, 10.5 and 6.5 Hz), 7.39 (1H, d, J=4.5 Hz), 7.55 (1H, t, J=7.5 Hz), 7.70 (1H, t, J=7.5 Hz), 7.90 (1H, d, J=8 Hz), 8.11 (1H, d, J=8.5 Hz), 8.87 (1H, d, J=4.5 Hz). ^{13}C NMR 24.8, 28.8, 28.9, 29.0, 29.1, 29.2, 62.3, 114.1, 122.9, 125.9, 126.9, 129.3, 130.2, 139.0, 141.1, 148.1, 150.1, 173.2. IR 1740. HRMS calculated for $C_{21}H_{27}NO_2$: 325.2042. Found: 325.2042.

4-Quinolylmethyl benzoate 8d.[17] Yield: 97%. ^{1}H NMR 5.84 (2H, s), 7.35–7.70 (5H, m), 7.76 (1H, td, J=7.5 and 1.5 Hz), 7.95–8.15 (3H, m), 8.21 (1H, d, J=8.5 Hz), 8.96 (1H, d, J=4.5 Hz). ^{13}C NMR 63.0, 119.7, 123.0, 127.2, 128.2, 128.5, 129.4, 129.6, 129.7, 129.9, 133.4, 141.5, 147.8, 150.0, 166.1. IR 1720. HRMS calculated for $C_{17}H_{13}NO_2$: 263.0946. Found: 263.0947.

4-Quinolylmethyl 4-cyanobenzoate 8e. Yield: 93%. ^{1}H NMR 5.86 (2H, s), 7.50 (1H, d, J=4.5 Hz), 7.62 (1H, t, J=7.5 Hz), 7.75 (2H, d, J=8+1H), 8.02 (1H, d, J=8 Hz), 8.17 (2H, d, J=8+1H), 8.93 (1H, d, J=4.5 Hz). ^{13}C NMR 63.9, 114.6, 117.8, 120.1, 122.8, 126.0, 127.3, 129.7, 130.3, 130.5, 132.4, 133.3, 140.2, 148.3, 150.2, 164.5. IR 1727, 2234. HRMS calculated for $C_{18}H_{12}N_2O_2$: 288.0899. Found: 288.0892.

4-Quinolylmethyl 4-bromobenzoate 8f. Yield: 93%. ^{1}H NMR 5.82 (2H, s), 7.50 (1H, d, J=4.5 Hz), 7.58 (2H, d, J=8.5 Hz), 7.61 (1H, t, J=8.5 Hz), 7.75 (1H, t, J=8.5 Hz), 7.94 (2H, d, J=8.5 Hz), 8.01 (1H, d, J=8.5 Hz), 8.16 (1H, d, J=8.5 Hz), 8.92 (1H, d, J=4.5 Hz). ^{13}C NMR 63.3, 119.9, 122.9, 126.0, 127.2, 128.5, 128.6, 129.5, 130.4, 131.2, 131.9, 140.7, 148.3, 150.2, 165.4. IR 1736. HRMS calculated for $C_{17}H_{12}BrNO_2$: 341.0052. Found: 341.0051.

4-Quinolylmethyl 4-formylbenzoate 8g. Yield: 95%. ^{1}H NMR 5.87 (2H, s), 7.53 (1H, d, J=4.5 Hz), 7.63 (1H, t, J=7.5 Hz), 7.76 (1H, t, J=7.5 Hz), 7.96 (2H, d, J=8.5 Hz), 8.03 (1H, d, J=9 Hz), 8.18 (1H, d, J=8.5 Hz), 8.24 (2H, d, J=8.5 Hz), 8.94 (1H, d, J=4.5 Hz), 10.09 (1H, s). ^{13}C NMR 63.6, 119.9, 122.8, 125.9, 127.2, 129.5, 130.26, 130.31, 134.3, 139.3, 140.4, 148.1, 150.2, 165.0, 191.4. IR 1707, 1728. HRMS calculated for $C_{18}H_{13}NO_3$: 291.0896. Found: 291.0895.

4-Quinolylmethyl 4-nitrobenzoate 8h. Yield: 93%. ^{1}H NMR 5.87 (2H, s), 7.51 (1H, d, J=4.5 Hz), 7.62 (1H, t, J=7.5 Hz), 7.76 (1H, t, J=7.5 Hz), 8.02 (1H, d, J=8.5 Hz), 8.17 (1H, d, J=8.5 Hz), 8.26 (4H, AB signal, J=9 Hz), 8.93 (1H, d, J=4.5 Hz). ^{13}C NMR 64.0, 120.1, 122.8, 123.7, 126.0, 127.3, 129.6, 130.5, 130.9, 134.8, 140.1, 148.3, 150.2, 150.7, 164.2. IR 1728. $C_{17}H_{12}N_2O_4$ calculated: C 66.23, H 3.92, N 9.09. Found: C 66.19, H 3.95, N 9.07.

4-Quinolylmethyl phenoxyethanoate 8i. Yield: 92%. ^{1}H NMR 4.70 (2H, s), 5.62 (2H, s), 6.8–7.0 (3H, m), 7.15–7.25 (2H, m), 7.28 (1H, d, *J*=4.5 Hz), 7.49 (1H, t, *J*=7.5 Hz), 7.67 (1H, t, *J*=7.5 Hz), 7.81 (1H, d, *J*=8.5 Hz), 8.11 (1H, d, *J*=8.5 Hz), 8.81 (1H, d, *J*=4.5 Hz). ^{13}C NMR 63.0, 65.3, 114.6, 119.9, 121.8, 122.7, 125.8, 127.0, 129.3, 129.4, 130.3, 140.0, 148.2, 150.0, 157.7, 168.5. IR 1727. HRMS calculated for $C_{18}H_{15}NO_3$: 293.1052. Found: 293.1049.

4-Quinolylmethyl 5-chloropentanoate 8j. Yield: 92%. ^{1}H NMR 1.65–1.90 (4H, m), 2.41 (2H, t, *J*=7 Hz), 3.46 (2H, t, *J*=6 Hz), 5.53 (2H, s), 7.36 (1H, d, *J*=4.5 Hz), 7.52 (1H, t, *J*=7.5 Hz), 7.67 (1H, t, *J*=7.5 Hz), 7.87 (1H, d, *J*=8.5 Hz), 8.08 (1H, d, *J*=8.5 Hz), 8.84 (1H, d, *J*=4.5 Hz). ^{13}C NMR 22.0, 31.6, 33.1, 44.2, 62.4, 119.6, 122.8, 125.8, 126.9, 129.3, 130.1, 140.8, 147.9, 150.0, 172.5. IR 1732. HRMS calculated for $C_{15}H_{16}ClNO_2$: 277.0870. Found: 277.0870.

4-Quinolylmethyl 7-oxooctanoate 8k. Yield: 95%. ^{1}H NMR 1.15–1.40 (2H, m), 1.45–1.70 (4H, m), 2.08 (3H, s), 2.30–2.50 (4H, m), 5.56 (2H, s), 7.40 (1H, d, *J*=4.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.71 (1H, t, *J*=7.5 Hz), 7.92 (1H, d, *J*=8 Hz), 8.12 (1H, d, *J*=8.5 Hz), 8.87 (1H, d, *J*=4.5 Hz). ^{13}C NMR 23.1, 24.5, 28.4, 29.8, 33.8, 43.2, 62.3, 119.7, 122.9, 125.9, 126.9, 129.4, 130.1, 141.0, 148.0, 150.1, 173.0, 208.7. IR 1714, 1736. HRMS calculated for $C_{18}H_{21}NO_3$: 299.1522. Found: 299.1520.

Ethyl 4-quinolylmethyl butanedioate 8l. Yield: 88%. ^{1}H NMR 1.16 (3H, t, *J*=7 Hz), 2.55–2.80 (4H, m), 4.06 (2H, q, *J*=7 Hz), 5.56 (2H, s), 7.40 (1H, d, *J*=4.5 Hz), 7.53 (1H, t, *J*=7.5 Hz), 7.68 (1H, t, *J*=7.5 Hz), 7.87 (1H, d, *J*=8.5 Hz), 8.10 (1H, d, *J*=8.5 Hz), 8.85 (1H, d, *J*=4.5 Hz). ^{13}C NMR 14.0, 28.88, 28.91, 60.7, 62.6, 119.6, 122.8, 125.8, 127.0, 129.4, 129.9, 140.9, 147.7, 149.9, 171.8, 172.0. IR 1731, 1733. HRMS calculated for $C_{16}H_{17}NO_4$: 287.1158. Found: 287.1147.

Preparation of 4-QUI esters 8m and 8n

To a CH_2Cl_2 (10 ml) solution of 4-quinolylmethanol **7** (159 mg, 1 mmol), DMAP (24 mg, 0.2 mmol) and Et_3N (340 μl, 2.4 mmol), sebacoyl chloride (240 μl, 1.1 mmol) was added dropwise. After stirring at room temperature during 4 h, benzyl (for **8m**) or allyl (for **8n**) alcohol (1 mmol) was added dropwise. The resulted mixture was stirred at room temperature during 24 h, when diluted with 30 ml of diethyl ether and washed with 2×30 ml water. The aqueous phases were extracted with 2×20 ml of diethyl ether and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 6/4).

Phenylmethyl 4-quinolylmethyl decanedioate 8m. Yield: 85%. ^{1}H NMR 1.10–1.40 (8H, m), 1.50–1.75 (4H, m), 2.32 (2H, t, *J*=7.5 Hz), 2.41 (2H, t, *J*=7.5 Hz), 5.09 (2H, s), 5.58 (2H, s), 7.25–7.40 (5H, m), 7.43 (1H, d, *J*=4.5 Hz), 7.59 (1H, t, *J*=7.5 Hz), 7.73 (1H, t, *J*=7.5 Hz), 7.94 (1H, d, *J*=8 Hz), 8.14 (1H, d, *J*=8.5 Hz), 8.90 (1H, d, *J*=4.5 Hz). ^{13}C NMR 24.9, 29.0, 34.2, 34.3, 62.4, 66.0, 119.8, 123.0, 126.1, 127.0, 128.1, 128.5, 129.4, 130.3, 136.3, 141.2, 148.3, 150.2, 173.2, 173.4. IR 1740. $C_{27}H_{31}NO_4$ calculated: C 74.80, H 7.21, N 3.23. Found: C 74.79, H 7.21, N 3.22.

Prop-2-enyl 4-quinolylmethyl decanedioate 8n. Yield: 90%. ^{1}H NMR 1.10–1.40 (8H, m), 1.50–1.75 (4H, m), 2.30 (2H, t, *J*=7.5 Hz), 2.41 (2H, t, *J*=7.5 Hz), 4.55 (2H, d, *J*=5.5 Hz), 5.20 (1H, dd, *J*=10.5 and 1 Hz), 5.28 (1H, dd, *J*=17 and 1 Hz), 5.58 (2H, s), 5.89 (1H, ddt, *J*=17, 10.5, and 5.5 Hz), 7.43 (1H, d, *J*=4.5 Hz), 7.58 (1H, t, *J*=7.5 Hz), 7.73 (1H, t, *J*=7 Hz), 7.93 (1H, d, *J*=8 Hz), 8.14 (1H, d, *J*=8 Hz), 8.90 (1H, d, *J*=4.5 Hz). ^{13}C NMR 24.6, 28.7, 33.8, 62.1, 64.6, 117.7, 119.4, 122.7, 125.7, 126.7, 129.1, 129.9, 132.1, 140.9, 147.8, 149.9, 172.9, 173.0. IR 1732, 1736. HRMS calculated for $C_{23}H_{29}NO_4$: 383.2097. Found: 383.2087.

Preparation of di (4-QUI) diester 8o

To a CH_2Cl_2 (10 ml) solution of 4-quinolylmethanol **7** (318 mg, 2 mmol), DMAP (24 mg, 0.2 mmol) and Et_3N (340 μl, 2.4 mmol), sebacoyl chloride (240 μl, 1.1 mmol) was added dropwise. After stirring at room temperature during 24 h, the resulted mixture was diluted with 30 ml of diethyl ether and washed with 2×30 ml water. The aqueous phases were extracted with 2×20 ml of diethyl ether and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 6:4).

Di(4-quinolylmethyl) decanedioate 8o. Yield: 85%. ^{1}H NMR 1.15–1.45 (8H, m), 1.55–1.75 (4H, m), 2.40 (4H, t, *J*=7.5 Hz), 5.58 (4H, s), 7.42 (2H, d, *J*=4.5 Hz), 7.59 (2H, t, *J*=7.5 Hz), 7.73 (2H, t, *J*=7.5 Hz), 7.93 (2H, d, *J*=8 Hz), 8.13 (2H, d, *J*=8.5 Hz), 8.89 (2H, d, *J*=4.5 Hz). ^{13}C NMR 24.8, 28.9, 34.1, 62.3, 119.7, 122.9, 125.9, 127.0, 129.4, 130.1, 141.1, 148.0, 150.1, 173.2. IR 1736. $C_{30}H_{32}N_2O_4$ calculated: C 74.35, H 6.66, N 5.78. Found: C 74.30, H 6.68, N 5.73.

Preparation of 1-NAP ester of *N*-Boc-L-Phe-OH 15

To a CH_2Cl_2 (75 ml) solution of *N*-Boc-L-Phe-OH **14** (1.33 g, 5 mmol) and 1-naphthylmethanol (0.79 g, 5 mmol) was added at 0°C a CH_2Cl_2 (10 ml) solution of DCC (1.25 g, 6 mmol). After stirring at 0°C during 2 h, the reaction mixture was filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 6:4) to give **15** (1.82 g, 4.5 mmol).

(2*S*) 1-Naphthylmethyl 2-[*N*-(1,1-dimethylethyl)oxycarbonyl]amino-3-phenylpropanoate 15. Yield: 90%. $[\alpha]_D^{20}=-13.78$ (c 1.56, methanol). ^{1}H NMR 1.39 (9H, s), 3.03 (2H, m), 4.60–4.70 (1H, m), 4.99 (1H, d, *J*=8 Hz), 5.60 (2H, AB signal, *J*=12.5 Hz), 6.85–7.10 (2H, m), 7.10–7.30 (3H, m), 7.45–7.65 (4H, m), 7.80–8.05 (3H, m). ^{13}C NMR 28.2, 38.1, 54.4, 65.2, 79.8, 123.4, 125.1, 125.9, 126.6, 126.8, 127.8, 128.3, 128.6, 129.2, 129.4, 130.7, 131.5, 133.6, 135.7, 155.0, 171.7. IR 3366, 1724, 1690. HRMS calculated for $C_{25}H_{27}NO_4$: 405.1940. Found: 405.1940.

Deprotection reactions

A typical procedure is as follows: compound **8** or **15** (1 mmol) in 1 ml of DMSO was added under argon to a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and dppe

(10 mg, 0.025 mmol) in 1 ml of DMSO. After 0.25 h stirring, this solution was added to a suspension of ammonium formate (252 mg, 4 mmol) in 2 ml of DMSO. The reaction mixture was stirred at 50°C for 12 h, cooled to room temperature, then 1 ml of 2 M Na_2CO_3 and 1 ml of iodomethane were added. After 24 h stirring, the reaction mixture was diluted with diethyl ether (10 ml) and washed with 2×20 ml water and with 2×20 ml 0.5% HCl. The aqueous phases were extracted with 20 ml of diethyl ether and the combined ethereal phases were dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (silica, heptane/ethyl acetate 8:2) to give products **9**, **10**, **11** or **16**. Yields are given in Table 1. Compounds **9** (except **9k**,[18] **9l**,[19] and **9m**) and **10** are commercially available. An authentic sample of compound **16** was prepared from **14** according to the literature.[20]

Methyl phenylmethyldecanedioate 9m. ^{1}H NMR 1.20–1.40 (8H, m), 1.50–1.70 (4H, m), 2.27 (2H, t, J=7.5 Hz), 2.33 (2H, t, J=7.5 Hz), 3.64 (3H, s), 5.09 (2H, s), 7.25–7.40 (5H, m). ^{13}C NMR 24.8, 28.9, 29.1, 34.0, 34.2, 51.3, 66.0, 128.1, 128.4, 136.0, 173.5, 174.1. IR 1736, 1739. HRMS calculated for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1830.

Methyl 4-quinolylmethyl decanedioate 11. ^{1}H NMR 1.15–1.40 (8H, m), 1.45–1.75 (4H, m), 2.27 (2H, t, J=7.5 Hz), 2.41 (2H, t, J=7.5 Hz), 3.64 (3H, s), 5.58 (2H, s), 7.42 (1H, d, J=4.5 Hz), 7.58 (1H, t, J=7.5 Hz), 7.73 (1H, t, J=7 Hz), 7.94 (1H, d, J=8 Hz), 8.13 (1H, d, J=8 Hz), 8.89 (1H, d, J=4.5 Hz). ^{13}C NMR 24.8, 29.0, 34.0, 34.1, 52.5, 62.4, 119.7, 123.0, 126.2, 127.0, 129.4, 130.2, 142.3, 147.8, 150.2, 173.3, 173.5. IR 1735, 1736. HRMS calculated for $C_{21}H_{27}NO_4$: 357.1940. Found: 357.1940.

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