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Direct Synthesis of Naltrexone by Palladium-Catalyzed *N*-Demethylation/Acylation of Oxymorphone: The Benefit of C–H Activation and the Intramolecular Acyl Transfer from C-14 Hydroxy

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Abstract: Oxymorphone was converted to naltrexone in three steps by palladium-catalyzed oxidative *N*-demethylation and intramolecular acyl transfer from C-14 hydroxy to N-17. Vitride™ reduction of *N*-acylamide to *N*-alkylamine proceeded with concomitant reductive deprotection of C-6 and O-3 functionalities.

Keywords: intramolecular acyl transfer; palladium-catalyzed *N*-demethylation; synthesis of naltrexone; Vitride™ reduction of amides

The synthesis of all opiate-derived analgesic agents and the various antagonists or mixed agonists currently used in medicine originates in naturally occurring alkaloids isolated from the opium poppy latex. The most commonly used are morphine and its congeners codeine, thebaine, and oripavine, shown in Figure 1.

There are two major challenges in the large-scale manufacture of the ubiquitously used pharmaceutical agents such as oxycodone, oxymorphone, naltrexone,[1,2] naloxone, and nalbuphone, shown in Figure 1. The first concerns the introduction of the C-14 hydroxy required for all of these compounds. This problem has been adequately solved by various oxidation protocols[3,4] and thebaine and oripavine lend themselves as convenient starting materials for the C-14 hydroxylated analogs. Thus one would not expect that much improvement could be incorporated into the manufacturing process save for completely new methods involving C–H activation or biological catalysis. The second challenge, much more difficult, requires the replacement of the *N*-methyl group of natural opiates with the *N*-cyclopropylmethyl, *N*-allyl, or *N*-cyclobutylmethyl functionality found in naltrexone, naloxone, and nalbuphone.

The *N*-demethylation protocols include the von Braun reaction (BrCN),[5] ethyl chloroformate,[6] demethylation of *N*-oxides,[7] and enzymatic methods.[8] The secondary amines are then converted to the desired products by alkylation. Because the synthesis of oxymorphone from oripavine or thebaine proceeds efficiently on the industrial scale we became interested

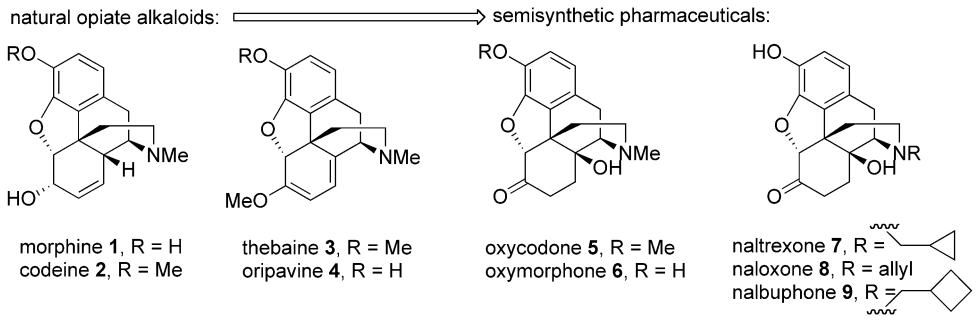


Figure 1. Natural opiates and their semisynthetic medicinal agents.

in the direct conversion of oxymorphone to naltrexone. This paper reports a reasonably improved synthesis of naltrexone from oxymorphone *via* an *N*-demethylation/acylation/reduction sequence.

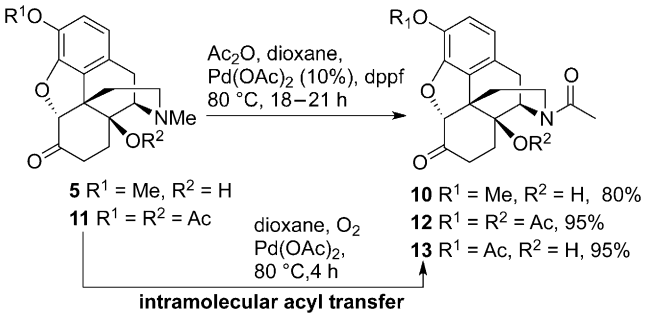
Metal-catalyzed oxidations of primary, secondary and tertiary amines are important transformations in organic chemistry, because the oxidation products such as nitriles, nitrones, imines, and iminiums are highly useful intermediates for the synthesis of biologically active nitrogen-containing compounds.[9] As aerobic oxidation represents a desirable protocol in view of green chemistry[10] many methods for metal-catalyzed aerobic oxidative transformations of primary amines to nitriles have been explored.[11] Catalytic aerobic oxidation of secondary amines to the corresponding imines is limited to a few systems,[12] and oxidations of tertiary amines were described in the literature as well.[13] Of special interest are the oxidations of tertiary amines with subsequent C–C[14] and C–heteroatom bond formation. These reactions, based on an initial C–H bond activation, have earned the attention of chemists because of the efficiency of formation of α-functionalized compounds from simple starting materials. Environmentally benign oxidants such as hydrogen peroxide, *tert*-butyl hydroperoxide, or oxygen, are usually employed.

The *N*-demethylation of tertiary amines is also important in metabolism where it is accomplished by cytochrome P-450 oxidation. The ruthenium-catalyzed *N*-demethylation of tertiary methylamines leads to α-*tert*-butyldioxymethylamines whose hydrolysis yields the secondary amines *via* iminium ions.[15] Several other catalytic and stoichiometric processes for *N*-demethylations have been reported.[16,17]

Our reported *N*-demethylation/acylation of hydrocodone and several tropane alkaloids by palladium catalysis in the presence of anhydrides failed with oxycodone.[17c] Ripper demonstrated a photochemical *N*-demethylation/acylation in modest yield where the acyl group was transferred from the pre-formed C-14-acyl ester.[18]

Returning to this problem, we discovered that the treatment of oxycodone with $Pd(OAc)_2$ and 5–10 mol% of free dppf ligand in dioxane at 80 °C led to *N*-acetyloxycodone **10** as a mixture of two amide rotamers in 80% yield, Scheme 1. [We did not observe axial and equatorial acetamides of **10**, as was the case with *N*-acetylhydrocodone, isolated as 3:1 mixture (eq/ax) and proven by X-ray analysis of the equatorial isomer and variable temperature NMR on the mixture.[17c]]

The presence of the free ligand was not important but the crucial parameter was the concentration and the presence of oxygen. Formation of a palladium black precipitate was a sign of a successful reaction.[19] This protocol was then applied to bis-*O*-acetyloxymorphone **11** to furnish the corresponding *N*-acetyl



Scheme 1.

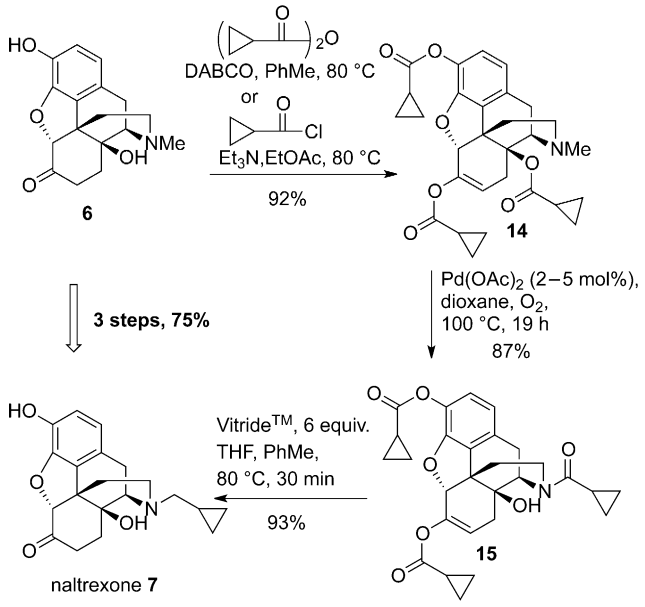
derivative **12** in 95% yield. When bis-*O*-acetyloxymorphone was subjected to the same conditions but in the absence of Ac_2O, *N*-acetyl derivative **13** was isolated in 95% yield, *via* an intramolecular migration. The intramolecular nature of this transfer was also shown by cross-over experiments on *O*-acetyl-14-acetoxyoxymorphone **11**, conducted in the presence of propionic acid anhydride at different concentrations. A mixture of *N*-acetyl and *N*-propionyl derivatives (major product at high concentrations of propionic acid anhydride) resulted.

This exciting result prompted the search for the optimum conditions for this process. The best yields were obtained with 2–5 mol% of $Pd(OAc)_2$, in dioxane and under an atmosphere of oxygen. The details of optimizations, ultimately leading to the anhydride-free acylation, are shown in Table 1 in the Supporting Information.

Amide **13** was subjected to hydrolysis (6 M HCl) and alkylation (NMP, H_2O, Et_3N, CPM-Br 1.5 equiv.) under literature conditions to yield the various *N*-alkyl derivatives, such as naltrexone, in *ca.* 90% yield.

A more expedient route to naltrexone was envisioned as a result of the observed intramolecular acyl transfer. Oxymorphone was peracylated with cyclopropylcarboxylic acid anhydride, or the less expensive acyl chloride, and converted to the fully acylated **14**. Exposure of **14** to the anhydride-free conditions of *N*-demethylation provided an excellent yield of amide **15**, whose reduction with Vitride™ furnished in 93% naltrexone **7** (Scheme 2).

In a more detailed investigation the *N*-demethylation of **14** was conducted in the absence of additional cyclopropylcarboxylic acid anhydride taking advantage of the intramolecular acyl transfer from the neighboring C-14 ester. A 92% yield of **15** was obtained with Pd(C) in dioxane in the presence of air at 100 °C. In a DMF-water mixture (5:1) and with $Pd(OAc)_2$ the yield of **15** was 95% after 23 h at 100 °C. A somewhat lower yield (85%, with 7–8% recovery of the starting material) was obtained when Pd(C) was employed in DMF-water. The reduction of **15** to naltrexone with Vitride™ is extremely fast be-



Scheme 2.

cause of the anchimeric assistance of C-14 hydroxy and an intramolecular reagent delivery.

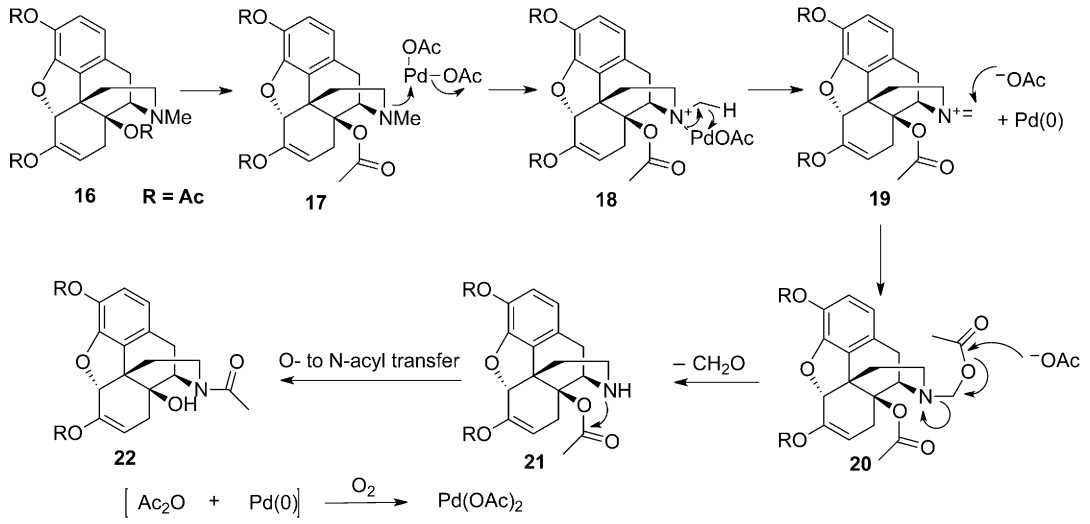
Vitride™ is a very convenient and inexpensive reducing agent, whose use at industrial scales is preferred to other, less safe, reducing agents such as lithium aluminum hydride.

The three-step transformation of oxymorphone to naltrexone proceeds with an overall yield of *ca.* 75% and can likely be further optimized, possibly even reduced to a one-pot procedure without isolation or purification. We propose a mechanism for the $Pd(OAc)_2$-catalyzed *N*-demethylation and intramolecular acyl transfer from C-14 to the nitrogen as shown in Scheme 3 (for alternative suggestions, including C–H activation, see Figures 2 and 3 in the Supporting Information).

The mechanism in Scheme 3 could apply to processes conducted in the presence of palladium acetate, recycled at the end of each turn-over. The reaction works equally well with Pd(C) in the presence of air and in the absence of any acyl donor except for the C-14 ester. [Tertiary amines are also oxidized with platinum in the presence of oxygen.[20]] Various options for the reactions of Pd(0) and Pd(II) with amines have been suggested in the literature and were reviewed.[21]

A process involving a C–H activation and the role of oxygen is depicted in Figure 4 in the Supporting Information (see als the suggested scheme and discussion therein). The key step may be the formation of a palladium π-complex of the iminium species bearing a Pd–H bond as a result of dehydrogenation[22] caused by Pd(0).[23] The coordination of the nitrogen with the low valent palladium and the overlap of the metal orbital with the α-C–H bond induces C–H activation and the formation of the η^2-iminium hydride metal complex, as was proven by racemization experiments at the chiral α carbon of tertiary amines and deuterium-labeling experiments at the α and β positions.[17a,23a] The isolation of such a Pd-iminium ion complex and its structure determination by X-ray diffraction were reported.[24] A similar C–H activation in a ruthenium cluster-catalyzed alkyl-exchange reaction was also demonstrated.[25] Such an activation is likely the key step in the asymmetric isomerization of allylamines to enamines in the industrially important chiral menthol synthesis.[26]

The oxidation of a metal hydride M–H species with molecular oxygen to give M–OOH species was demonstrated in the asymmetric oxypalladation of allylphenols,[27] in the palladium-catalyzed aerobic oxida-



Scheme 3.

tion of alcohols,[28] and in the ruthenium-catalyzed oxidative transformation of primary amines to nitriles.[11g] Subsequent reaction of [iminium]-PdOOH species with a suitable nucleophile (water or dioxane) then provides a hemiaminal and a palladium hydroperoxide species. An oxopalladium(II) species is obtained and this intermediate reacts with the tertiary amine to give [iminium ion]-PdOH by an electron transfer and a subsequent hydrogen transfer. The [iminium ion]-PdOH is trapped with water to afford the hemiaminal, low valent palladium, and a molecule of water to complete the catalytic cycle.

Naltrexone was prepared in three steps and 75% overall yield from oxymorphone *via* an intramolecular acyl transfer from C-14 hydroxy to the nitrogen atom following the palladium-catalyzed *N*-demethylation. The cyclopropylcarboxamide is then reduced with excess Vitride™, along with the ester protecting groups at C-3 and C-6. At industrial scales the by-product, cyclopropylmethyl alcohol (2 equivalents) could be recycled through oxidation. The generality of this process and the mechanistic details involved in the *N*-demethylation/acylation protocol will be further investigated. Alternative methods for the reduction of amides, such as hydrosilylation protocols,[29,30] should be compared for overall efficiency.

Experimental Section

3,6,14-Tris(cyclopropylcarboxy)oxymorphone (14)

The suspension of oxymorphone (1.56 g, 5.19 mmol), cyclopropylcarboxylic acid anhydride (4.0 g; 25.9 mmol), and toluene (20 mL) was stirred at 80 °C for 160 min. DABCO (1.16 g, 10.4 mmol) was added in one portion and the resulting mixture was stirred at 80 °C for 15 h. After this time the conversion was incomplete and an additional amount of cyclopropylcarboxylic acid anhydride (1.60 g, 10.4 mmol) was added and the mixture was stirred at 80 °C for 5 h. The reaction mixture was allowed to cool to room temperature, concentrated under vacuum, and the excess anhydride was removed under high vacuum. The mixture was diluted with dichloromethane (20 mL), washed with saturated $NaHCO_3$ (5 mL) and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. Silica gel chromatography (EtOAc→EtOAc/MeOH 9:1) afforded **14** as a white solid; yield: 2.37 g (90%); mp 158–160 °C (EtOH); R_f=0.40 (EtOAc/hexane 1:1); $[\alpha]_D^{20}$: −122.96 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν=3025, 2934, 2849, 1743, 1716, 1440, 1387, 1100, 1032 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=6.86 (d, J=8.2 Hz, 1H), 6.67 (d, J=8.2 Hz, 1H), 5.42 (dd, J=6.0, 1.6 Hz, 1H), 5.08 (s, 1H), 4.22 (d, J=6.0 Hz, 1H), 3.21 (d, J=18.8 Hz, 1H), 3.05 (dd, J=18.3, 6.2 Hz, 1H), 2.55 (dd, J=18.8, 6.2 Hz, 1H), 2.47 (dd, J=11.8, 4.7 Hz, 1H), 2.38 (ddd, J=12.3, 12.3, 5.2 Hz, 1H), 2.31 (s, 3H), 2.22 (ddd, J=12.0, 12.0, 3.4 Hz, 1H), 2.04 (d, J=18.4 Hz, 1H), 1.87 (m, 1H), 1.77–1.69 (m, 1H), 1.65–1.58 (m, 2H), 1.21 (m, 1H), 1.18 (m, 1H), 1.14–1.09 (m, 3H), 1.05 (m, 1H), 1.04–1.00 (m, 2H), 0.99–0.94 (m, 2H), 0.90–0.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.08, 173.21, 172.47, 147.37, 143.85, 133.30, 131.59, 130.69, 122.69, 118.87, 116.56, 86.88, 81.02, 57.45, 47.06, 45.07, 42.87, 30.28, 27.27, 22.96, 14.52, 12.97, 12.81, 9.367, 9.23, 9.16, 9.05, 8.55, 8.43; MS (+EI): *m/z* (%)=41 (48), 56 (55), 69 (100), 86 (100), 124 (20), 167 (16), 437 (16), 505 (12); HR-MS: *m/z*=505.21049, calcd. for $C_{29}H_{31}NO_7$: 505.2101.

3,6,17-Tris(cyclopropylcarboxy)noroxymorphone (15)

A mixture of perprotected oxymorphone **14** (1.0 g, 1.9 mmol), $Pd(OAc)_2$ (0.009 g; 0.004 mmol), and dioxane (10 mL) was stirred at 100 °C for 24 h under an oxygen atmosphere. After 5 min of stirring a thick Pd black precipitate was observed. Once TLC analysis indicated the consumption of **14** the mixture was concentrated and purified by silica gel chromatography (EtOAc) to afford **15** as a mixture of amide isomers (1:4) that was easily crystallized; yield: 0.85 g (87%); mp 130–133 °C (MeOH); R_f=0.46 (EtOAc); IR ($CHCl_3$): ν=3573, 3419, 3013, 2919, 1747, 1618, 1448, 1386, 1149, 1032 cm^{-1}.

Major isomer: ^1H NMR (600 MHz, $CDCl_3$): δ=6.89 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 5.53 (s, 1H), 5.10 (m, 1H), 5.07 (s, 1H), 4.07 (d, J=11.0 Hz, 1H), 3.30–3.13 (m, 2H), 2.89 (d, J=18.6 Hz, 1H), 2.51 (m, 1H), 2.24 (m, 1H), 2.17 (m, 1H), 1.86 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.65 (m, 1H), 1.24–1.14 (m, 2H), 1.09 (m, 2H), 1.05 (m, 2H), 1.00–0.91 (m, 4H), 0.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.07, 173.17, 172.48, 147.69, 143.44, 133.59, 131.05, 130.05, 123.08, 119.19, 117.26, 86.72, 71.24, 53.62, 47.44, 38.73, 32.71, 32.44, 29.37, 12.95, 12.81, 11.75, 9.39, 9.27, 9.17, 9.05, 7.76, 7.41.

Minor isomer: ^1H NMR (600 MHz, $CDCl_3$): δ=6.89 (d, J=8.0 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 5.53 (s, 1H), 5.01 (s, 1H), 4.47 (m, 1H), 3.27 (m, 1H), 3.03 (d, J=18.3 Hz, 1H), 2.65 (dd, J=12.0, 11.0 Hz, 1H), 2.38–2.12 (m, 3H), 1.90–1.63 (m, 4H), 1.24–1.14 (m, 2H), 1.09 (m, 2H), 1.05 (m, 2H), 1.00–0.91 (m, 4H), 0.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=174.07, 173.35, 172.39, 147.69, 143.69, 133.69, 131.05, 129.52, 123.21, 119.19, 117.15, 86.60, 71.11, 57.52, 47.58, 34.79, 33.11, 32.14, 28.64, 12.95, 12.81, 11.75, 9.39, 9.27, 9.17, 9.05, 7.77, 7.22; MS (+EI): *m/z* (%)=41 (36), 69 (100), 112 (9), 226 (6), 294 (3), 354 (4), 423 (5), 491 (10); HR-MS: *m/z*=491.19479, calcd. for $C_{28}H_{29}NO_7$: 491.1944.

Naltrexone (7)

A flame-dried flask was thoroughly purged with nitrogen and charged with Vitride™ (0.76 g of 65% solution in toluene, 2.44 mmol). A solution of amide **15** (0.20 g, 0.41 mmol) in THF (2 mL) was added over 30 sec. When bubbling ceased the mixture was placed into a pre-heated oil bath at 80 °C. After refluxing for 30 min the mixture was allowed to cool to room temperature, quenched with a cold solution of Rochelle salt (2 mL), water (2 mL), and diluted with dichloromethane (3 mL). After extraction and the separation of organic layers a saturated solution of NH_4Cl (0.5 mL) was added to the aqueous layers and **7** was extracted with dichloromethane. The addition of a solution of NH_4Cl (0.5 mL) and extraction sequence was repeated three times. The combined organic layers were washed with water, brine,

dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (EtOAc/MeOH 4:1) to afford naltrexone (**7**) as a white solid; yield: 0.13 g (93%); mp 159–161 °C (MeOH), [lit. mp 174–176 °C (acetone)[31]]; $R_f = 0.42$ (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$: −207.00 (*c* 1, $CHCl_3$); IR ($CHCl_3$): $\nu = 3568, 3359, 3010, 2931, 2834, 1723, 1620, 156, 1317, 1146, 1058, 943\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.74$ (d, $J = 8.1$ Hz, 1H), 6.60 (d, $J = 8.1$ Hz, 1H), 5.82 (bs, 1H, OH), 4.74 (s, 1H), 3.21 (d, $J = 5.9$ Hz, 1H), 3.11–3.03 (m, 2H), 2.72 (dd, $J = 12.0$, 4.8 Hz, 1H), 2.58 (dd, $J = 18.4$, 6.0 Hz, 1H), 2.49–2.39 (m, 3H), 2.34 (ddd, $J = 14.5$, 3.0, 3.0 Hz, 1H), 2.18 (ddd, $J = 12.2$, 3.8, 3.8 Hz, 1H), 1.91 (m, 1H), 1.66 (ddd, $J = 14.2$, 14.2, 3.3 Hz, 1H), 1.59 (ddd, $J = 12.8$, 2.7 Hz, 1H), 0.88 (m, 1H), 0.57 (m, 2H), 0.16 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 210.02$, 142.51, 138.80, 129.05, 124.25, 119.90, 117.91, 90.60, 70.32, 62.01, 59.21, 51.07, 43.60, 36.21, 31.36, 30.65, 22.62, 9.42, 4.02, 3.81; MS (+EI): *m/z* (%) = 47 (15), 55 (41, 84 (100), 110 (12), 202 (5), 256 (12), 286 (7), 300 (15), 341 (64); HR-MS; *m/z* = 341.16320, calcd. for $C_{20}H_{23}NO_4$: 341.1627.

Supporting Information

Experimental and spectral data for compounds **7**, **11**, **12**, **13**, **14**, and **15** are available in the Supporting Information. In addition, details of the optimization of the Pd-catalyzed N-demethylation as well as alternative suggestions for the mechanism of intramolecular acyl transfer are included.

Acknowledgements

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