Pd/C-Catalyzed Chemoselective Hydrogenation in the Presence of a Phenolic MPM Protective Group Using Pyridine as a Catalyst Poison

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Employment of a Pd/C–pyridine combination as a catalyst is a very useful method for the selective removal (hydrogenolysis) of phenolic *O*-benzyl, *N*-Cbz and benzyl ester protective groups and for the selective hydrogenation of nitro and olefin functions of phenol derivatives protected with the MPM group. These discriminatory results are apparently attributable to the effect of pyridine. The MPM group could be extensively applied to chemoselective hydrogenation as a protective group for phenolic hydroxyl functions.

Key words Pd/C; chemoselectivity; MPM ether; hydrogenation; pyridine; catalyst poison

While numerous methods are reported in the literature for the reduction using Pd/C, selective hydrogenation of reducible functionalities, such as olefin, Cbz protective group, benzyl ester and nitro group, in the presence of a benzyl ether has not been fully addressed.[1—3] Benzyl protection of a hydroxyl group is a widely used protective method in synthetic chemistry because of the chemical stability and the mild conditions involved in its removal by catalytic hydrogenolysis.[4] A few selective reductions of other reducible functionalities were previously accomplished in the presence of a benzyl ether by catalytic hydrogenation using a heterogeneous catalyst.[5—8] Recently, we also found that addition of a nitrogen-containing base such as ammonia, triethylamine, pyridine, ammonium acetate, to a Pd/C-catalyzed reduction system selectively suppressed the hydrogenolysis of an aliphatic benzyl ether with smooth hydrogenation of other reducible functionalities such as olefin, *N*-Cbz, benzyl ester and azido.[9—11] However, the selective suppression of hydrogenolysis using mild catalyst poisons was not applicable to the benzyl protective group for phenolic hydroxyl functions. During the course of our further study on the Pd/C-catalyzed chemoselective hydrogenolysis, we found a significant difference in the suppressive effect on the hydrogenolysis of phenolic *O*-benzyl protective groups depending upon the nitrogen-containing bases employed as an additive. By using a Pd/C–2,2′-dipyridyl combination as a catalyst for the hydrogenation, both aliphatic and phenolic *O*-benzyl protective groups can be ultimately retained without any hydrogenolysis.[10—12] On the other hand, we continuously investigated further applicable procedures for a chemoselective hydrogenation without the hydrogenolysis of a benzyl-type protective group on phenolic hydroxyl functions. Herein, we report the chemoselective suppression of the hydrogenolysis of the *p*-methoxybenzyl (MPM) protective group for phenolic hydroxyl functions under the Pd/C-catalyzed hydrogenation conditions in the presence of pyridine as a mild catalyst poison.[6]

Our initial studies were conducted using Boc–Tyr(Bn)–OMe (**1**)[11] as the reactant. The hydrogenolysis of the phenolic benzyl ether of **1** was examined with different additives to form Boc–Tyr–OMe (**2**), and the time course on the hydrogenolysis (balloon) of **1** using 5% Pd/C plus 0.5 eq of ammonia or pyridine is shown in Fig. 1. The phenolic benzyl ether of **1** could be rapidly cleaved within 2 h under both hydrogenolysis conditions. However, the stronger suppressive effect of pyridine toward the hydrogenolysis became apparent by detailed monitoring of the reaction progress (Fig. 1).

It would be strongly desirable to develop a range of benzyl-type protective groups possessing different stabilities against the Pd/C-catalyzed hydrogenolysis. There is only one effective report for the chemoselective suppression of the hydrogenolysis of phenolic benzyl ethers using a sterically hindered 2,4-dimethylbenzyl group although the suppressive effect is not perfect.[14] These results had led us to investigate whether a combination of the addition of pyridine and the electronic or steric properties of the benzyl group can control the rate of cleavage, which should derive the hydrogenolysis-resistant benzyl protective groups of phenolic hydroxyl groups.

Hydrogenolysis of several 1,4-dibenzyloxybenzene derivatives (**3a**—**f**) was carried out using 5% Pd/C and pyridine combination (Table 1). The reaction was carried out under ordinary hydrogen pressure (balloon) using 0.5 eq of pyridine and 5% Pd/C (10% of the weight of **3a**—**f**) in MeOH at room temperature (rt) for 24 h. The products distributions were calculated based on the integration ratio of each peak of TLC scanner (Shimadzu CS-9000) and were corrected by molar extinction coefficients of the substrates **3a**—**f**, the

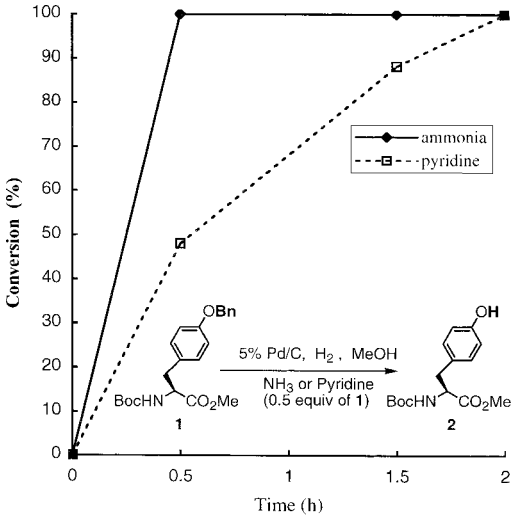

Fig. 1. Time Course on the Hydrogenolysis (Balloon) of **1** at Room Temperature Using 5% Pd/C in the Presence of Ammonia or Pyridine

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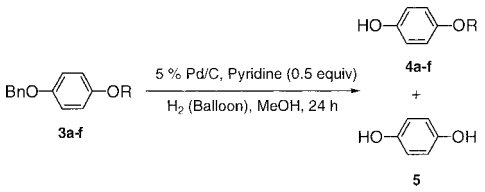
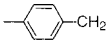
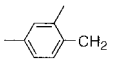
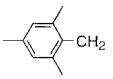
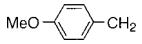
products **4a**—**f** and **5**. As shown in Table 1, the hydrogenolysis of substituted benzyl-type groups of **3b**—**f** was especially depressed by the addition of pyridine while at least one benzyl protective group of **3a**—**f** was entirely hydrogenolyzed for 24 h in each case. It is interesting to note that the hydrogenolysis of the 2,4,6-trimethylbenzyl group and *p*-methoxybenzyl (MPM) group was perfectly suppressed under the reaction conditions (entries 5, 6). It is possible that pyridine can compete with the 2,4,6-trimethylbenzyl group and the MPM group for the active sites on the palladium. This was also strongly suggested in a control experiment where hydrogenolysis of substrates **3a**—**f** without pyridine proceeded much more smoothly (Table 1, the products ratios in parentheses). The suppressive effect of the hydrogenolysis of substituted benzyl-type groups of **3b**—**f** can be ascribed to the electronic properties of the methyl and methoxy substituents on the benzene ring rather than the steric hindrance effect of methyl groups on the *ortho* positions of **3c**—**e** since the introduction of the second methyl group on the *para* position of the benzene ring was much more effective in suppressing the hydrogenolysis (compare entries 3 and 4) than the introduction of an *ortho* methyl group (compare entries 2 and 3). This study identifies that the two major factors controlling the hydrogenolysis of the 2,4,6-trimethylbenzyl or MPM protective group are the affinity of pyridine for the palladium surface and the inhibitory action on the palladium surface (active site)–benzylic site conjugation by the electronic properties of the 2,4,6-trimethylbenzyl group and the MPM group.

Table 1. Effect of the Substituents on the Aromatic Ring of Benzyl Group toward the Hydrogenolysis of **3a**—**f**



Entry	Substrate (**3**)	R	Products ratio[a,b] **4** : **5**
1	**3a**	Bn	17 : 83 (0 : 100)
2	**3b**		52 : 48 (0 : 100)
3	**3c**		32 : 68 (0 : 100)
4	**3d**		90 : 10 (60 : 40)
5	**3e**		100 : 0 (89 : 11)
6	**3f**		100 : 0 (49 : 51)

a) Reactions were followed by TLC scanner (Shimadzu CS-9000). *b*) The products ratios in parenthesis were obtained without pyridine.

The present suppression method for the deprotection of the 2,4,6-trimethylbenzyl or MPM group of the phenolic hydroxyl group can be applied to the selective hydrogenation of some substrates which possess other reducible functionalities, such as phenolic benzyl ether, *N*-Cbz, benzyl ester, nitro, or olefin functions, within the molecule. For synthetic purposes, it would be desirable to find a new protective group which is more stable under various synthetic conditions but more labile under the special deprotection process. We anticipate that the MPM group, a popular protective group of alcohols and phenols,[15,16] would fulfill these criteria, and it was chosen as a benzyl-type protective group for further investigation because of its chemical stability and concise and wide variety of procedures for the deprotection (DDQ or CAN oxidation,[17] TFA treatment,[18] $NaBH_3CN$–$BF_3 \cdot Et_2O$ reduction,[19] and Pd/C-catalyzed hydrogenation[17]).

To investigate the synthetic utility of these results, the selective removal of MPM and benzyl groups was conducted on substrates **6** (Chart 1). The results show that the benzyl group of **6** can be cleanly removed from the phenolic hydroxyl group without deprotection of the MPM group to give **7** in 96% yield as the sole product. Though the debenzylation was completed within 1 h, the reaction was allowed to stand for 24 h to prove the selectivity of the deprotection (hydrogenolysis). The control experiment of the dipeptide, Boc–Tyr(Bn)–Thr(MPM)–OMe (**6**) under the hydrogenolysis conditions without pyridine results in the complete cleavage of both benzyl and MPM ethers to give the corresponding Boc–Tyr–Tyr–OMe (**8**) in 78% yield (Chart 1).

To explore the generality of the chemoselective hydrogenation of MPM ether derivatives some substrates possessing other reducible functionalities were studied using 5% Pd/C in the presence of 0.5 eq of pyridine. As shown in Table 2, the selective hydrogenolysis of *O*-Bn (entry 1), benzyl ester (entry 4) and *N*-Cbz (entry 5) protective groups and the selective hydrogenation of nitro (entry 3) and olefin (entry 2) functionalities were entirely successful on substrates coexisting with a phenolic *O*-MPM protective group. The MPM

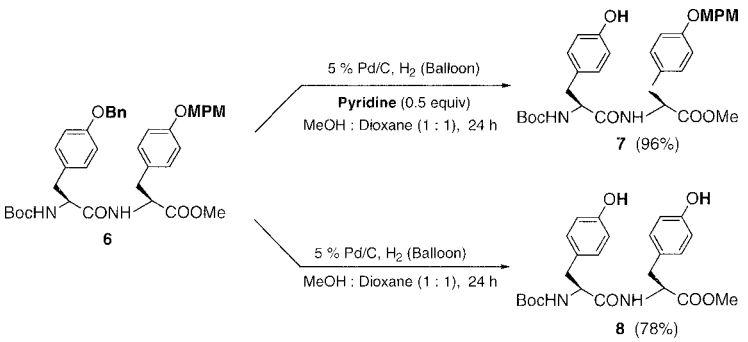
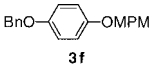
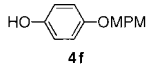
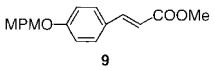
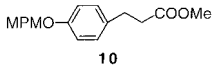
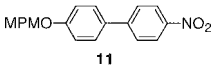
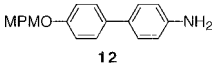
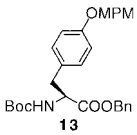
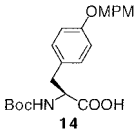
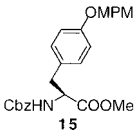
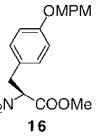


Chart 1

Table 2. Chemoselective Hydrogenation Phenolic MPM Ethers in the Presence of Pyridine

Entry	Substrate (ROMPM)	Solvent	Reaction time (h)	Product	Yield (%)[a]
1	 **3f**	MeOH	24[b]	 **4f**	98
2	 **9**	DMF	2	 **10**	96
3	 **11**	DMF	1	 **12**	94
4	 **13**	MeOH : Dioxane (1 : 1)	24[c]	 **14**	95
5	 **15**	MeOH : Dioxane (1 : 1)	24[d]	 **16**	86

a) Isolated yield. *b*) Reaction was completed within 5 h by TLC scanner (Shimadzu CS-9000). *c*) Reaction was completed within 1 h by TLC scanner. *d*) Reaction was completed within 2.5 h by the TLC scanner.

groups can be thoroughly tolerated under the 5% Pd/C–pyridine catalyzed hydrogenolysis conditions and the desired product **4f**, **7**, **10**, **12**, **14** or **16** was obtained in excellent isolated yield in each case.

In summary, we have described a novel and chemoselective hydrogenation method in the presence of phenolic MPM ethers. While 5% Pd/C-catalyzed hydrogenolysis can be generally used for removal of MPM protective groups,[15,17] the addition of pyridine as a mild catalyst poison absolutely suppresses the hydrogenolysis of the phenolic *O*-MPM protective group.[20] By using the 5% Pd/C–pyridine system as a catalyst for the hydrogenation, the phenolic *O*-MPM protective group can be retained without hydrogenolysis. The reaction is general for a variety of phenolic *O*-MPM ethers, and the method would increase the utility of the MPM protective group in synthetic chemistry.

Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Column chromatography was carried out under air by flash method described by Still[21] with silica gel (230—400 mesh, Merck). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F_{254}, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. UV spectra were measured in EtOH with Shimadzu UV-260 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL GX-270 (270 MHz) or JEOL EX-400 (400 MHz). Chemical shifts are given in parts per million from Me_4Si as the internal standard in $CDCl_3$ and coupling constants (*J*) were reported in hertz (Hz). Low- and high-resolution mass spectra (LR- and HR-MS) were taken on a JMS-SX 102A machine. Microanalyses were accomplished at the Microanalytical Laboratory of Gifu Pharmaceutical University.

Time Course of Hydrogenation of *N*-Boc-*O*-benzyl-L-tyrosine Methyl Ester (1) Monitored by a TLC Scanner (Fig. 1) A mixture of **1**[11] (38.5 mg, 0.10 mmol), ammonia or pyridine (0.05 mmol), 5% Pd/C (3.9 mg) and MeOH (1 ml) was stirred under hydrogen atmosphere (balloon) at rt (*ca.* 20 °C). Reaction progress was monitored by TLC Scanner (Shimadzu CS-9000) at 275 nm (*Rf* value of **1**: 0.65, *Rf* value of **2**: 0.39, ether : hexane = 2 : 1). The yields were calculated on the integration ratio of each peak, which were corrected by molar extinction coefficients of **1** and **2**.

1,4-Dibenzyloxybenzene (3a) To a stirred mixture of 4-benzyloxyphenol (**4a**) (1.00 g, 4.99 mmol) and NaH (60% w/w in mineral oil, 0.20 g, 5.00 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (5 ml) was added benzyl bromide (0.59 ml, 5.00 mmol) dropwise at rt. The mixture was stirred at rt for 10 h, after which it was concentrated *in vacuo*. The residue was partitioned between ether (50 ml) and water (50 ml). The ethereal layer was washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated *in vacuo* to leave a solid residue, which was recrystallized from MeOH, providing **3a** (1.39 g, 97%): mp 125—126 °C. ^{1}H-NMR (400 MHz) δ: 5.02 (4H, s), 6.91 (4H, s), 7.32—7.44 (10H, m). UV λ_{max} (MeOH) nm (ε): 288 (2410), 226 (15600). LR-MS (EI) *m/z*: 290 (M^+). *Anal.* Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.66; H, 6.29.

1-Benzyloxy-4-(4-methylbenzyloxy)benzene (3b) Compound **3b** was prepared from 4-benzyloxyphenol (**4a**) (5.00 g, 24.97 mmol), 4-methylbenzyl bromide (4.63 g, 25.00 mmol) and NaH (60% w/w in mineral oil, 1.00 g, 25.00 mmol) in anhydrous DMF (20 ml) by the procedure described for the preparation of **3a** (7.48 g, 98%): mp 123—124 °C. ^{1}H-NMR (400 MHz) δ: 2.35 (3H, s), 4.97 (2H, s), 5.01 (2H, s), 6.90 (4H, s), 7.18 (2H, d, J=7.8 Hz), 7.30—7.33 (3H, m), 7.36—7.43 (4H, m). UV λ_{max} (MeOH) nm (ε): 289 (2680), 223 (19000). LR-MS (EI) *m/z*: 304 (M^+). *Anal.* Calcd for $C_{21}H_{20}O_2 \cdot 1/10H_2O$: C, 82.38; H, 6.65. Found: C, 82.44; H, 6.66.

1-Benzyloxy-4-(2-methylbenzyloxy)benzene (3c) Compound **3c** was prepared from 4-benzyloxyphenol (**4a**) (3.09 g, 15.40 mmol), 2-methylbenzyl bromide (2.08 ml, 15.50 mmol) and NaH (60% w/w in mineral oil, 0.62 g, 15.50 mmol) in anhydrous DMF (5 ml) by the procedure described for the preparation of **3a** (4.13 g, 88%): mp 92.5—93.5 °C. ^{1}H-NMR (400 MHz) δ: 2.52 (3H, s), 5.12 (2H, s), 5.15 (2H, s), 7.08 (4H, s), 7.38—7.42 (3H, m), 7.45—7.59 (6H, m). UV λ_{max} (MeOH) nm (ε): 288 (2720). LR-MS (EI) *m/z*: 304 (M^+). *Anal.* Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.67; H, 6.69.

1-Benzyloxy-4-(2,4-dimethylbenzyloxy)benzene (3d) Compound **3d** was prepared from 4-benzyloxyphenol (**4a**) (1.00 g, 4.99 mmol), 2,4-dimethylbenzyl chloride (purity 90%, 0.81 ml, 5.00 mmol) and NaH (60% w/w in mineral oil, 0.20 g, 5.00 mmol) in anhydrous DMF (5 ml) by the procedure described for the preparation of **3a** (1.57 g, 99%): mp 72—73 °C (hexanes). ^{1}H-NMR (270 MHz) δ: 2.32 and 2.33 (each 3H, s), 4.94 and 5.02 (each 2H, s), 6.91 (4H, s), 7.01 (2H, d, J=9.4 Hz), 7.28—7.44 (6H, m). UV λ_{max} (MeOH) nm (ε): 288 (1370), 225 (13500). LR-MS (EI) *m/z*: 318 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.99; H, 6.97.

1-Benzyloxy-4-(2,4,6-trimethylbenzyloxy)benzene (3e) Compound **3e** was prepared from 4-benzyloxyphenol (**4a**) (1.00 g, 4.99 mmol), 2,4,6-trimethylbenzyl chloride (0.84 g, 5.00 mmol) and NaH (60% w/w in mineral oil, 0.20 g, 5.00 mmol) in anhydrous DMF (5 ml) by the procedure described for the preparation of **3a** (1.57 g, 95%): mp 83—84 °C (hexanes). ^{1}H-NMR (400 MHz) δ: 2.27 (3H, s), 2.34 (6H, s), 4.94 and 5.02 (each 2H, s), 6.91

(2H, s), 6.93 (4H, s), 7.31—7.44 (5H, m). UV λ_{max} (MeOH) nm (ε): 288 (2600), 227 (26300). LR-MS (EI) *m/z*: 332 (M^+). *Anal.* Calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.29; H, 7.38.

1-Benzyloxy-4-(4-methoxybenzyloxy)benzene (3f) To a stirred mixture of 4-benzyloxyphenol (**4a**) (1.00 g, 4.99 mmol) and NaH (60% w/w in mineral oil, 0.20 g, 5.00 mmol) in anhydrous DMF (5 ml) was added 4-methoxybenzyl chloride (0.67 ml, 5.00 mmol) dropwise at rt. The mixture was stirred at rt for 10 h, after which it was concentrated *in vacuo*. The residue was triturated with ether and H_2O and the resulting solid product was collected by filtration, which was recrystallized from MeOH–AcOEt, providing **3d** (1.57 g, 98%): mp 137.5—138.5°C. ^{1}H-NMR (270 MHz) δ: 3.81 (3H, s), 4.93 and 5.01 (each 2H, s), 6.90 (4H, s), 6.91 (2H, d, J=6.8 Hz), 7.30—7.45 (7H, m). UV λ_{max} (MeOH) nm (ε): 281 (3040), 229 (26700). LR-MS (EI) *m/z*: 320 (M^+). *Anal.* Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.51; H, 6.16.

Hydrogenation of 3a—d Monitored by a TLC Scanner (Table 1) After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of **3** (0.1 mmol), 5% Pd/C (10% of the weight of the substrate **1**) in MeOH (1 ml) with or without pyridine (0.05 mmol) was stirred under hydrogen atmosphere (balloon) at rt (*ca.* 20 °C) for 24 h. Reaction progress was monitored by TLC Scanner (Shimadzu CS-9000). The yields were calculated on the integration ratio of each peak, which were corrected by molar extinction coefficients of **4a**—**f** and hydroquinone (**5**). If the isolation of the product (**4**) was necessary to measure the molar extinction coefficients, the reaction mixture was filtered using a membrane filter (Millipore Dimex-13, 0.22 mm), the filtrate was concentrated, and the residue was purified by silica gel column chromatography to provide pure **4**.

4-Benzyloxyphenol (**4a**)[22]: UV λ_{max} (EtOH) nm (ε): 291 (2610), 225 (9980).

4-(4-Methylbenzyloxy)phenol (**4b**): mp 154.5—155.5 °C. ^{1}H-NMR (400 MHz) δ: 2.35 (3H, s), 4.39 (1H, s), 4.96 (2H, s), 6.75 and 6.85 (each 2H, d, J=8.8 Hz), 7.18 and 7.31 (each 2H, d, J=7.8 Hz). UV λ_{max} (MeOH) nm (ε): 291 (2560), 221 (14600). LR-MS (EI) *m/z*: 214 (M^+). *Anal.* Calcd for $C_{14}H_{14}O_2 \cdot 1/10H_2O$: C, 77.83; H, 6.62. Found: C, 78.06; H, 6.61.

4-(2-Methylbenzyloxy)phenol (**4c**): mp 105—106 °C. ^{1}H-NMR (400 MHz) δ: 2.37 (3H, s), 4.40 (1H, s), 4.97 (2H, s), 6.77 and 6.88 (each 2H, d, J=8.8 Hz), 7.21—7.25 (3H, m), 7.39 (1H, d, J=6.8 Hz). UV λ_{max} (MeOH) nm (ε): 291 (2560). LR-MS (EI) *m/z*: 214 (M^+). *Anal.* Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.32; H, 6.64.

4-(2,4-Dimethylbenzyloxy)phenol (**4d**): ^{1}H-NMR (400 MHz) δ: 2.32 and 2.34 (each 3H, s), 4.93 (2H, s), 6.76 and 6.86 (each 2H, d, J=9.0 Hz), 7.01 (2H, d, J=7.6 Hz), 7.03 (1H, s), 7.26 (2H, d, J=7.6 Hz). UV λ_{max} (MeOH) nm (ε): 291 (3750), 222 (22300). LR-MS (EI) *m/z*: 228 (M^+). HR-MS (EI) *m/z*: 228.1145 (Calcd for $C_{15}H_{16}O_2$: 228.1150).

4-(2,4,6-Trimethylbenzyloxy)phenol (**4e**): ^{1}H-NMR (400 MHz) δ: 2.29 (3H, s), 2.36 (6H, s), 4.90 (1H, br, deuterium exchangeble), 4.95 (2H, s), 6.77 and 6.90 (each 2H, d, J=8.8 Hz), 6.91 (2H, s). UV λ_{max} (MeOH) nm (ε): 291 (3110), 224 (20600). LR-MS (EI) *m/z*: 242 (M^+). HR-MS (EI) *m/z*: 242.1318 (Calcd for $C_{16}H_{18}O_2$: 242.1307).

4-Methoxybenzyloxyphenol (**4f**): mp 136—137 °C. ^{1}H-NMR (400 MHz) δ: 3.81 (3H, s), 4.49 (1H, s), 4.93 (2H, s), 6.75 and 6.85 (each 2H, d, J=8.8 Hz), 6.91 and 7.34 (each 2H, d, J=8.5 Hz). UV λ_{max} (MeOH) nm (ε): 282 (1380), 222 (10500). LR-MS (EI) *m/z*: 230 (M^+). HR-MS (EI) *m/z*: 230.0939 (Calcd for $C_{14}H_{14}O_3$: 230.0943). *Anal.* Calcd for $C_{14}H_{14}O_3 \cdot 1/3H_2O$: C, 71.17; H, 6.26. Found: C, 71.30; H, 6.07.

Hydroqinone (**5**)[22]: UV λ_{max} (EtOH) nm (ε): 293 (2900), 224 (5300).

Boc–Tyr(Bn)–Tyr(MPM)–OMe (6) To a solution of Boc–Tyr(Bn)–OH (37.1 mg, 0.1 mmol)[22] and diphenylphosphorylazide (DPPA, 22.6 μl, 0.11 mmol) in DMF (0.25 ml) a solution of H–Tyr(MPM)–OMe **16** (32.7 mg, 0.1 mmol) in DMF (0.25 ml) was added dropwise at 0 °C. The mixture was stirred at rt for 12 h and then poured into ice-cooled phosphate buffer solution (pH 7.0, 10 ml). The resulting mixture was extracted with AcOEt (10 ml) and the organic layer was washed with H_2O (10 ml) and brine (10 ml) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by flash silica gel column chromatography ($CHCl_3$), providing **6** (63.5 mg, 95%): mp 164—165 °C. ^{1}H-NMR (270 MHz) δ: 1.39 (9H, s), 2.89—3.04 (4H, m), 3.67 and 3.81 (each 3H, s), 4.23—4.38 and 4.72—4.80 (each 1H, m), 4.93 (2H, d, J=3.4 Hz), 5.02 (2H, s), 6.29 (1H, br), 6.83—6.92 (8H, m), 7.09 (2H, dd, J=8.3, 6.4 Hz), 7.31—7.42 (7H, m). LR-MS (FAB) *m/z*: 669 (M^++1). *Anal.* Calcd for $C_{39}H_{44}N_2O_8$: C, 70.04; H, 6.63; N, 4.19. Found: C, 69.81; H, 6.58; N, 4.21.

4-(4-Methoxybenzyloxy)cinnamic Acid Methyl Ester (9)[12] To a stirred mixture of 4-hydroxycinnamic acid methyl ester (1.78 g, 10.00 mmol) and NaH (60% w/w in mineral oil, 0.44 g, 11.00 mmol) in anhydrous DMF (15 ml) was added 4-methoxybenzyl chloride (1.49 g, 11.00 mmol) dropwise at 0 °C. The mixture was stirred at rt for 12 h, and the reaction mixture was poured into ice-water. The mixture was extracted with AcOEt (30 ml) and the organic layer was washed with H_2O (30 ml) and brine (30 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography ($CHCl_3$), providing analytically pure **9** (2.44 g, 82%): mp 158—159 °C (MeOH). ^{1}H-NMR (400 MHz) δ: 3.79 and 3.82 (each 3H, s), 5.02 (2H, s), 6.31 (1H, d, J=16.1 Hz), 6.92, 6.97, 7.35 and 7.47 (each 2H, d, J=8.8 Hz), 7.65 (1H, d, J=16.1 Hz). LR-MS (FAB) *m/z*: 298 (M^+). *Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.42; H, 6.14.

4-(4-Methoxybenzyloxy)-4′-nitrobiphenyl (11) Compound **11** was prepared from 4-hydroxy-4′-nitrobiphenyl (0.22 g, 1.00 mmol), 4-methoxybenzyl chloride (0.16 ml, 1.18 mmol) and NaH (60% w/w in mineral oil, 80 mg, 2.00 mmol) in anhydrous DMF (5 ml) by the procedure described for the preparation of **9** (0.31 g, 93%): ^{1}H-NMR (270 MHz) δ: 3.83 (3H, s), 5.06 (2H, s), 6.94, 7.08, 7.38, 7.58, 7.69 and 8.27 (each 2H, d, J=8.8 Hz). LR-MS (EI) *m/z*: 335 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.56; H, 5.15; N, 4.14.

Boc–Tyr(MPM)–OBn (13) Compound **13** was prepared from Boc–Tyr–OBn (0.74 g, 2.00 mmol),[22] 4-methoxybenzyl chloride (0.30 ml, 2.21 mmol) and NaH (60% w/w in mineral oil, 84 mg, 2.10 mmol) in anhydrous DMF (2 ml) by the procedure described for the preparation of **9** (0.97 g, 98%): mp 89—90 °C. ^{1}H-NMR (400 MHz) δ: 1.42 (9H, s), 3.02 (2H, br d, J=5.9 Hz), 3.82 (3H, s), 4.46—4.63 (1H, m), 4.95 (2H, s), 4.97 (1H, br), 5.13 (2H, dd, J=22.5, 12.2 Hz), 6.82 (2H, d, J=8.3 Hz), 6.87—6.95 (5H, m), 7.28—7.36 (7H, m). LR-MS (EI) *m/z*: 491 (M^+). HR-MS (EI) *m/z*: 491.2319 (Calcd for $C_{29}H_{33}NO_6$: 491.2308). *Anal.* Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.72; H, 6.84; N, 2.87.

Cbz–Tyr(MPM)–OMe (15) A mixture of Cbz–Tyr–OH (4.40 g, 13.95 mmol)[22] and *N*,*N*-dimethylformamide dimethylacetal (2.78 ml, 20.86 mmol) in anhydrous DMF (10 ml) was stirred at rt for 15 h and the light yellow solution was poured into ice-water. The mixture was extracted with AcOEt (200 ml) and the organic layer was washed with H_2O (200 ml×2) and brine (15 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The colorless waxy product, Cbz–Tyr–OMe,[22] was used for the next reaction without further purification (3.53 g, 77%): ^{1}H-NMR (400 MHz) δ: 3.08—3.12 (3H, m, br), 3.79 (3H, s), 4.68 (1H, dd, J=8.3, 4.4 Hz), 5.11 (2H, br s), 5.16 (2H, d, J=4.4 Hz), 5.27 (1H, br d, J=8.3 Hz), 6.78 and 7.01 (each 2H, d, J=8.3 Hz), 7.38—7.42 (5H, m).

To a stirred mixture of Cbz–Tyr–OMe (see above, 3.53 g, 10.72 mmol) and NaH (60% w/w in mineral oil, 0.47 g, 11.80 mmol) in anhydrous DMF (10 ml) was added 4-methoxybenzyl chloride (1.60 ml, 11.80 mmol) dropwise at 0 °C. The mixture was stirred at rt for 2 h, and the reaction mixture was poured into ice-water. The mixture was extracted with AcOEt (50 ml) and the organic layer was washed with H_2O (50 ml) and brine (50 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexanes to hexanes : ether=1 : 1) to give a pale yellow waxy solid. The solid product was triturated with hexanes (50 ml) and the resulting colorless solid was collected by filtration, which was washed with hexanes (20 ml×3), providing analytically pure **15** (4.34 g, 90%): mp 82—83 °C. ^{1}H-NMR (270 MHz) δ: 3.03—3.05 (2H, m), 3.72 and 3.82 (each 3H, s), 4.61—4.64 (1H, m), 4.95 and 5.10 (each 2H, s), 5.15—5,21 (1H, m), 6.87, 6.91 and 7.00 (each 2H, d, J=8.8 Hz), 7.34—7.36 (7H, m). LR-MS (FAB) *m/z*: 450 (M^++1). *Anal.* Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.42; H, 6.25; N, 3.19.

General Procedure for the Chemoselective Hydrogenation of 3d, 6, 9, 11, 13 and 15 Using a Pd/C–Pyridine System (the Preparation of Compounds 4d, 7, 10, 12, 14 and 16, Chart 1 and Table 2) After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate (0.1 mmol), 5% Pd/C(en) (10% of the weight of the substrate) and pyridine (4 μl, 0.05 mmol, 0.5 eq of the substrate) in MeOH (1.0 ml), MeOH (0.5 ml)+dioxane (0.5 ml) or DMF (1.0 ml) depending on the solubility of the substrate was hydrogenated at ordinary pressure (balloon) and temperature (*ca.* 20 °C) for the appropriate time (see Chart 2 and Table 2). The reaction mixture was filtered using a membrane filter (Millipore Dimex-13, 0.22 μm) and the filtrate was concentrated *in vacuo*. The resulting product was purified by flash silica gel column chromatography, if necessary.

Boc–Tyr–Tyr(MPM)–OMe (**7**): NMR (270 MHz) δ: 1.42 (9H, s), 2.92—3.00 (4H, m), 3.68 and 3.82 (each 3H, s), 4.20—4.36 and 4.68—4.82 (each 1H, m), 4.95 (2H, s), 6.21 (1H, br), 6.71 (2H, d, J=8.3 Hz), 6.82—6.93 (6H, m), 7.02 (2H, d, J=7.3 Hz), 7.35 (2H, d, J=8.3 Hz). LR-MS (FAB) *m/z*: 579 (M^++1). HR-MS (FAB) *m/z*: 579.2724 (Calcd for $C_{32}H_{39}N_2O_8$: 579.2706).

4-(4-Methoxybenzyloxy)dihydrocinnamic Acid Methyl Ether (**10**)[12]: ^{1}H-

NMR (270 MHz) δ: 2.60 and 2.89 (each 2H, t, J=7.7 Hz), 3.67 and 3.82 (each 3H, s), 496 (2H, s), 6.89, 6.91, 7.11 and 7.35 (each 2H, d, J=8.8 Hz). LR-MS (EI) m/z: 298 (M^+), HR-MS (EI) m/z: 300.1356 (Calcd for $C_{18}H_{20}O_4$ 300.1362).

4-Amino-4′-(4-methoxybenzyloxy)biphenyl (**12**): ^{1}H-NMR (270 MHz) δ: 3.68 (2H, br), 3.82 (3H, s), 5.02 (2H, s), 6.74 (2H, d, J=8.8 Hz), 6.92 (2H, d, J=8.3 Hz), 7.00 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.3 Hz), 7.38 (2H, d, J=8.8 Hz), 7.45 (2H, d, J=8.3 Hz). LR-MS (EI) m/z: 305 (M^+). HR-MS (EI) m/z: 305.1425 (Calcd for $C_{20}H_{19}NO_2$: 305.1416).

Boc–Tyr(MPM)–OH (**14**): ^{1}H-NMR (400 MHz) δ: 1.42 (9H, s), 2.98—3.19 (2H, m), 3.81 (3H, s), 4.50—4.58 (1H, m), 4.96 (2H, s), 6.72 (1H, br), 6.90 (2H, d, J=7.6 Hz), 6.91 (2H, d, J=8.5 Hz), 7.00 (1H, br), 7.09 (2H, d, J=7.6 Hz), 7.34 (2H, d, J=8.5 Hz). LR-MS (FAB) m/z: 402 (M^++1). HR-MS (FAB) m/z: 402.1911 (Calcd for $C_{22}H_{28}NO_6$: 402.1917).

Tyr(MPM)–OMe (**16**): ^{1}H-NMR (400 MHz) δ: 2.79 (1H, dd, J=13.7, 7.8 Hz), 3.00 (1H, dd, J=13.7, 5.4 Hz), 3.58—3.70 (1H, m), 3.69 and 3.79 (each 3H, s), 4.94 (2H, s), 6.88 (2H, d, J=8.3 Hz), 6.89 (2H, d, J=8.8 Hz), 7.08 (2H, d, J=8.3 Hz), 7.32 (2H, d, J=8.8 Hz). LR-MS (EI) m/z: 315 (M^+). HR-MS (EI) m/z: 315.1459 (Calcd for $C_{18}H_{21}NO_4$: 315.1471).

Boc–Tyr–Tyr–OMe (8) After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of Boc–Tyr(Bn)–Tyr(MPM)–OMe **6** (67 mg, 0.1 mmol), 5% Pd/C(en) (7 mg) and pyridine (4 μl, 0.05 mmol) in MeOH (1.0 ml) and dioxane (1.0 ml) was hydrogenated at ordinary pressure (balloon) and temperature (*ca.* 20 °C) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore Dimex-13, 0.22 μm) and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography ($CHCl_3$: MeOH = 50 : 1), providing analytically pure **8** (36 mg, 78%): ^{1}H-NMR (270 MHz) δ: 1.42 (9H, s), 2.87—2.93 (4H, m), 3.69 (3H, s), 4.20—4.35 (1H, m), 4.68—4.82 (1H, m), 5.22 (1H, br), 6.67 (1H, br), 6.53—6.91 (8H, m). LR-MS (FAB) m/z: 459 (M^++1). HR-MS (FAB) m/z: 459.2125 (Calcd for $C_{24}H_{31}N_2O_7$: 459.2131).

References and Notes

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