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Microbial *C*-hydroxylation and β-4-*O*-methylglucosidation of methyl-benzamide 7-azanorbornane ethers with *Beauveria bassiana*

Horacio F. Olivo [a,*], Tonya L. Peeples [b], María-Yolanda Ríos [a], Francisco Velázquez [a], Jin-Woo Kim [b], Someet Narang [b]

[a] *Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA*
[b] *Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, IA 52242, USA*

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Abstract

N-Substituted 7-azanorbornanes were prepared by acylation of easily accessible 7-azanorbornane hydrochloride. Derivatives possessing an electron-withdrawing docking/protecting group and bearing an aryl methylether were subjected to biotransformation with the fungus *Beauveria bassiana* ATCC 7159. *O*-Demethylation and β-4-*O*-methylglucosidation reactions were observed for the major metabolite in this biotransformation (isolation yields: **6**, 30%; **11a**, 44%; **11b**, 47%; **11c**, 14%). *C*-Hydroxylation on an unfunctionalized carbon was also observed in most of the cases.

Keywords: 7-Azanorbornanes; *C*-Hydroxylation; *O*-Demethylation; β-4-*O*-Methylglucosidation; *Beauveria bassiana*

1. Introduction

The use of selected microorganisms in the biotransformation of xenobiotics to effectively mimic the mammalian metabolism of drugs and natural products was introduced by Rosazza and Smith [1]. Microbial transformations have also proved valuable in obtaining good amounts of metabolites in a practical fashion [2]. The use of microbial transformations for the preparation of key synthetic intermediates has become a powerful technique that is particularly useful for the synthesis of valuable compounds that otherwise would take more efforts to synthesize. The filamentous fungus *Beauveria bassiana* ATCC 7159 has become a very popular microorganism among synthetic organic chemists because of its wide variety of substrate specificity and wide spectrum of activity [3].

We recently reported the microbial hydroxylation of an unfunctionalized carbon, using *B. bassiana*, for the synthesis of an important intermediate in the total synthesis of the natural alkaloid epibatidine [4]. *C*-Hydroxylation occurred on a methylene carbon when an electron-withdrawing docking/protecting group was present on a 7-azanorbornane. The biotransformation occurred with excellent stereocontrol in good to very good yields. However, the hydroxylation reaction showed poor enantioselectivity. We decided to explore the concept of a chiral auxiliary as a docking/protecting group in the biohydroxylation of 7-azanorbornanes. This concept was applied recently by de Raadt et al. [5] in the biohydroxylation

* Corresponding author.
E-mail address: horacio-olivo@uiowa.edu (H.F. Olivo).

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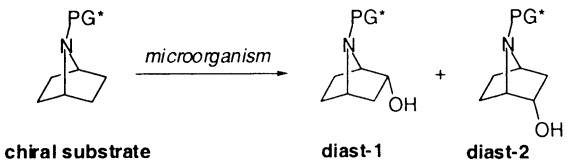
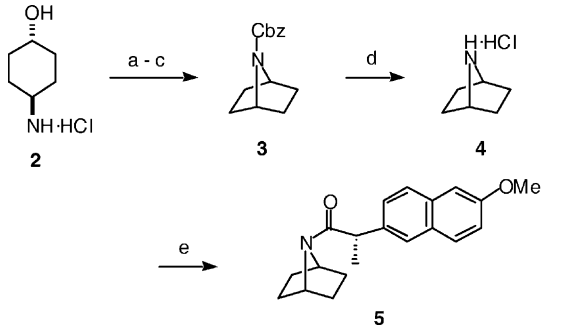
of spiro-oxazolidines derived from cyclopentanone.



2. Results and discussion

We envisioned that a chiral naproxen moiety could be a simple and practical auxiliary group to investigate in the biotransformation of a 7-azanorbornane. The preparation of 7-azanorbornane (**4**) required four simple steps and one column chromatographic purification from commercially available *trans*-4-aminocyclohexanol hydrochloride (**2**), Scheme 1. Naproxen was converted into the corresponding acid chloride [6], and added to 7-azanorbornane (**4**) to furnish substrate (**5**) in excellent yield.[1]

The naproxen substrate **5** was fed to the fungi *B. bassiana* using the fermentation technique previously described [4a]. The biotransformation proceeded to completion and a major metabolite was isolated in good yield (30% isolated yield). ^{1}H NMR spectroscopy of the major metabolite showed peaks corresponding to intact protons of the 7-azanorbornane and the naproxen ring, plus a doublet at 5.05 ppm, and signals from 3.9 to 3.2 ppm corresponding to six protons and a broad peak that integrated for three more protons. ^{13}C NMR spectroscopy showed peaks corresponding to the naproxen substrate plus five methine carbons between 100.7 and 74.0 ppm, and a methylene carbon at 62 ppm. These signals were indicative of the presence of a sugar. All the coupling constants of the sugar moiety corresponded to *trans*-diaxial protons. The amide metabolite was reduced with lithium aluminum hydride to obtain the corresponding tertiary amine (**7**) in order to facilitate its characterization, Scheme 2.[2] Acetylation of the metabolite confirmed the presence of three free hydroxyl groups in the sugar portion of the metabolite. The location



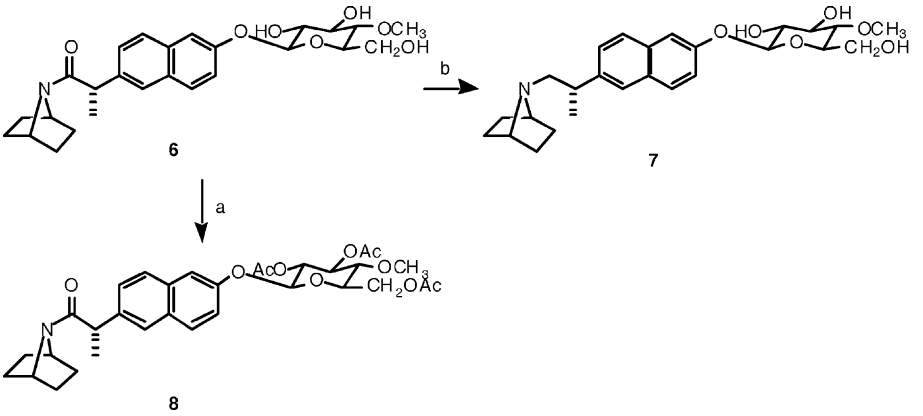
Scheme 1. Reagents and conditions: (a) Cbz-Cl, Et_3N, CH_2Cl_2. (b) Ms-Cl, Et_3N, CH_2Cl_2. (c) KO^tBu, DMF-C_6H_6 (1:1), 80–85% from **2**. (d) H_2, Pd/C, MeOH, HCl, 99%. (e) Naproxen acid chloride, Et_3N, CH_2Cl_2, 98%.

of the methyl group and the glucose was determined by HMBC experiments. Structure **6** revealed that an *O*-demethylation of the methyl ether carbon in the naproxen ring and 4-methyl-β-glucosidation on the phenolic oxygen preferentially occurred in the biotransformation. A small amount of *C*-hydroxylated metabolite was also isolated, but separation of the diastereomers by FCC was not successful. A continuous problem in using whole-cell biotransformations is that a number of possible transformations are feasible due to the presence of different enzymes in the cells. Although using a structural substrate comparison approach to select the microorganism that most probably will be valuable to effect the desired biotransformation can be successful, this method may lead to unexpected results.

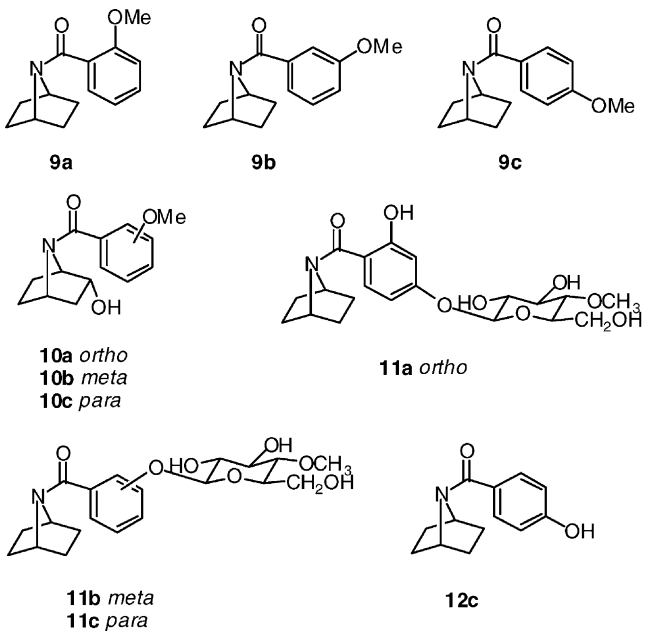
Thus, we decided to prepare the three anisoyl-7-azanorbornane derivatives, and study the applicability of these biotransformations with *B. bassiana*. *N*-Anisoyl-7-azanorbornane derivatives **9a–c** (Scheme 3) were readily prepared in excellent yield by addition of the corresponding acid chloride to 7-azanorbornane (**4**). The results of the biotransformation of anisoyl substrates **9a–c** with *B. bassiana* are illustrated in Table 1. In all the three cases, at least two metabolites from each biotransformation were isolated and characterized (Scheme 3). The 4-methylglucoside metabolites **11a** and **b** were observed as the major metabolites, except for the *para*-anisoyl derivative. In the case of the *ortho*-anisoyl substrate **9a**, the *O*-demethylated product could not be glucosidated because of the hydrogen bridge formed between the

[1] See Section 4.

[2] Enantiomeric excess was determined by derivatization of the alcohols **13a–c** with a Mosher acid chloride, after reduction of the amide **10a–c** with lithium aluminum hydride.



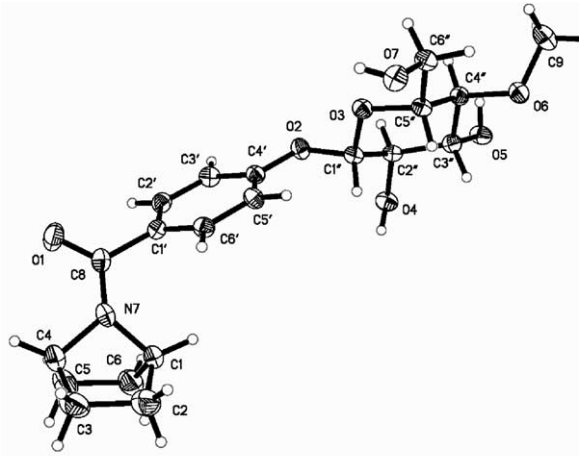
Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, 98%. (b) $LiAlH_4$, THF, reflux, 97%.



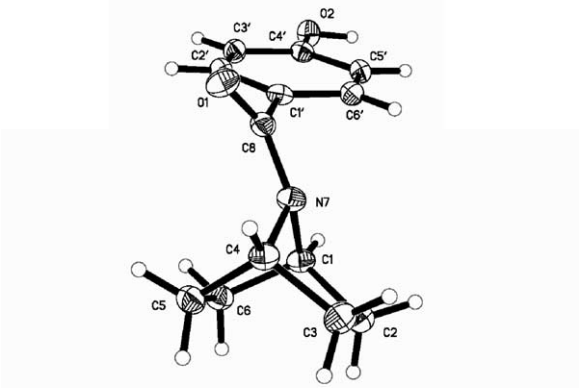
Scheme 3. X-ray crystal structure for metabolite **11c**.

Table 1
Biotransformation of *N*-Anisoyl-7-azanorbornanes

Substrate **9**	*C*-Hydroxylation **10** (%)	*O*-Glucoside **11** (%)	Phenol **12** (%)
a	42 (60% ee)	44	–
b	21 (15% ee)	47	–
c	41 (19% ee)	14	8



X-Ray crystal structure for metabolite **11c**



X-Ray crystal structure for metabolite **12c**

Scheme 4. X-ray crystal structure for metabolite **12c**.

phenolic and the amide groups. Instead, this product was oxidized on the *para*-position and glucosidated to give metabolite **11a**. *C*-Hydroxylation occurred with excellent stereocontrol in all the three cases (only the endo-alcohols were obtained), but with rather low enantioselectivity. The highest enantiomeric excess was observed for the *ortho*-anisoyl alcohol **10a**. In the case of *para*-anisoyl substrate **9c**, the *O*-demethylated metabolite **12c** was also isolated. X-ray crystal structures for metabolites **11c** and **12c** were determined to confirm the structural assignments, Scheme 4.

Microbial *O*-demethylation with *B. bassiana* ATCC 7159 has been previously observed in a methyl alkyl ether β-lactam [7] and in a methyl ether anthracycline [8]. β-4-*O*-Methylglucosidation with *B. bassiana* has been more commonly observed in the biotransformation of substrates containing a phenolic oxygen [9]. However, this study seems to be the first one, where all the three oxidative and β-4-*O*-methylglucosidation reactions occur on the same substrate.

3. Conclusion

In summary, we showed four examples of amides containing a methylaryl ether whose biotransformation with *B. bassiana* metabolized them to the β-4-methylglucoside after *O*-demethylation, together with their corresponding *C*-hydroxylated metabolite. These metabolic reactions appear to be general to methylaryl ethers and should be added to the arsenal of microbial reactions used to mimic human metabolic transformations [10].

4. Experimental

4.1. Instruments

General procedures. Both ^{1}H and ^{13}C NMR spectra were obtained using either a Bruker DRX-400 or WM-360 spectrometer, using TMS as internal reference in $CDCl_3$. Carbon multiplicities were determined using DEPT experiment. IR spectra were recorded using a Nicolet 210 spectrometer. Melting points reported here are not corrected. Melting points were obtained in a Thomas Hoover melting point apparatus. Optical rotations were measured with a Jasco P-1020 polarimeter. Analytical TLC were performed using pre-coated silica gel 60 F254 Merck plates. Elemental analyses were performed by Galbraith Laboratories Inc. (Knoxville, TN).

General procedure for the biotransformation of N-substituted 7-azanorbornanes [4a]. Cultures of ATCC 7159 were grown at 28 °C for 7 days. Stage I cultures were grown from agar slants in 25 ml of medium A (20 g of corn steep liquor, 10 g of D-glucose per liter of water, pH adjusted to 5.0) in 125 ml shake flasks at 250 rpm and 28 °C for 72 h. Stage II cultures were grown from Stage I cultures in 200 ml of medium A in 1 l shake flasks. After 24 h of growth,

the substrate (100 mg per flask) was added as a solution in ethanol or DMF. After 5–7 days of shaking, the cells were removed by vacuum filtration. The filtrate was saturated with NaCl and extracted a few times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography.

N-Naproxenyl-7-azanorbornane (**5**). A solution of 7-azanorbornane hydrochloride (1.336 g, 10 mmol) and triethylamine (3.036 g, 30 mmol) in 50 ml of dichloromethane, was treated with naproxene acid chloride (2.984 g, 12 mmol) in 10 ml of dichloromethane. The mixture was stirred at 0 °C for 6 h. The reaction was quenched with 100 ml of water, and the product was extracted with dichloromethane. The organic layer was washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using 35% ethyl acetate in hexanes to give compound **5** as a white solid (3.032 g, 98% yield). TLC: R_f = 0.27 (6.5:3.5, hexane/ethyl acetate); mp 115 °C; $[\alpha] = +30.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.68 (1H, δ, J = 8.5 Hz), 7.66 (2H, bs), 7.41 (1H, dd, J = 8.5, 1.5 Hz), 7.12 (1H, dd, J = 8.8, 2.5 Hz), 7.10 (1H, bd, J = 2.5 Hz), 4.68 (1H, bs), 4.20 (1H, bs), 3.90 (3H, s), 3.89 (1H, q, J = 6.9 Hz), 1.78 (2H, m), 1.60–1.20 (4H, m), 1.50 (3H, d, J = 6.9 Hz), 1.10 (1H, m), 0.82 (1H, m); ^{13}C NMR ($CDCl_3$): δ 169.9 (CO), 157.7 (C), 137.6 (C), 133.5 (C), 129.2 (CH), 129.1 (C), 127.4 (CH), 126.1 (CH), 125.5 (CH), 118.9 (CH), 105.6 (CH), 55.8 (CH), 55.3 (CH_3), 53.3 (CH), 44.7 (CH), 30.8 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 20.1 (CH_3); EIMS 310 (M + H+, 89), 277 (20); *Elementary Analysis*: Calculated for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.01; H, 7.53; N, 4.50.

*N-(2′S)-[6″-(4‴-O-Methyl-β-*D*-glucopyranosyl)-2″-naphthalene]-propionyl-7-azanorbornane* (**6**). TLC: R_f = 0.32 (9:1, dichloromethane/methanol); $[\alpha] = -36.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.65 (3H, m), 7.38 (1H, d, J = 8.5 Hz), 7.29 (1H, d, J = 2.0 Hz), 7.19 (1H, dd, J = 8.9, 2.0 Hz), 5.01 (1H, d, J = 7.2 Hz), 4.65 (1H, bs), 4.18 (1H, bs), 3.89 (2H, m), 3.80–2.80 (2H, bs), 3.72 (3H, m), 3.57 (3H, s), 3.45 (1H, m), 3.28 (1H, dd, J = 9.3, 8.7 Hz), 1.77 (2H, bs), 1.60–1.30 (4H, m), 1.50 (3H, d, J = 6.9 Hz), 1.26 (1H, m), 1.11 (1H, m), 0.86 (1H, m); ^{1}H NMR (CD_3OD): δ 7.75 (3H, m), 7.45 (1H, d, J = 2.4 Hz), 7.40 (1H, dd, J = 8.5, 1.6 Hz), 7.28 (1H, dd, J = 8.9, 2.4 Hz), 5.03 (1H, d, J = 7.7 Hz), 4.56 (1H, t, J = 4.6 Hz), 4.37 (1H, t, J = 4.6 Hz), 4.07 (1H, q, J = 6.9 Hz), 3.89 (1H, dd, J = 12.1, 2.0 Hz), 3.72 (1H, dd, J = 12.1, 4.9 Hz), 3.60 (3H, s), 3.62–3.40 (3H, m), 3.22 (1H, dd, J = 9.6, 9.0 Hz), 1.83 (1H, m), 1.73 (1H, m), 1.50–1.25 (3H, m), 1.45 (3H, d, J = 6.9 Hz), 1.20 (2H, m), 0.84 (1H, m); ^{13}C NMR ($CDCl_3$): δ 170.0 (CO), 154.8 (C), 138.4 (C), 133.2 (C), 130.2 (C), 129.5 (CH), 127.9 (CH), 126.5 (CH), 125.5 (CH), 119.1 (CH), 111.1 (CH), 100.7 (CH), 79.1 (CH), 76.7 (CH), 75.7 (CH), 74.0 (CH), 62.0 (CH_2), 60.9 (CH_3), 56.1 (CH), 53.5 (CH), 44.7 (CH), 30.9 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 20.0 (CH_3); IR (film): 3388, 2979, 1608, 1456, 1215. HRMS: Calculated for $C_{26}H_{33}NO_7 + H^+$: 472.2335. Found: 472.2351.

*N-(2′S)-[6″-(4‴-O-Methyl-β-*D*-glucopyranosyl)-2″-naphthalene]-propyl-7-azanorbornane* (**7**). A solution of amide **6** (20.0 mg, 0.042 mmol) in 5 ml of THF, was treated with lithium aluminum hydride (20 mg, 0.53 mmol) at 0 °C. The resulting suspension was heated to reflux overnight. Reaction was quenched by addition of a small amount of saturated Na_2SO_4 solution and heated to reflux for 15 min. The reaction mixture was filtered through celite and the solvent evaporated. The residue was purified by flash column chromatography on silica gel eluting with a mixture of dichloromethane–methanol–ammonia (80:10:1). The amine **7** was isolated as a clear oil (18 mg, 97% yield). $[\alpha] = +69$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.66 (2H, m), 7.60 (1H, s), 7.32 (2H, m), 7.19 (1H, dd, J = 9.2, 2.5 Hz), 5.02 (1H, d, J = 7.2 Hz), 3.93–3.08 (3H, bs), 3.88 (1H, m), 3.71 (3H, bs), 3.57 (3H, s), 3.43 (1H, m), 3.28 (1H, m), 3.15 (3H, m), 2.63 (2H, d, J = 6.8 Hz), 1.69 (4H, m), 1.35 (3H, d, J = 6.7 Hz), 1.19 (4H, m); ^{13}C NMR ($CDCl_3$): δ 154.5 (C), 142.6 (C), 133.1 (C), 130.3 (C), 129.5 (CH), 127.4 (CH), 126.7 (CH), 125.5 (CH), 118.9 (CH), 111.2 (CH), 100.7 (CH), 79.1 (CH), 76.6 (CH), 75.8 (CH), 73.9 (CH), 62.0 (CH_2), 61.0 (CH_3), 60.6 (2CH), 55.2 (CH_2), 40.3 (CH), 28.6 ($2CH_2$), 28.0 ($2CH_2$), 20.8 (CH_3); HRMS: Calculated for $C_{26}H_{35}NO_6 + H^+$: 458.2543. Found: 458.2548.

*N-(2′S)-[6″-(4‴-O-Methyl-2‴,3‴,6‴-triacetyl-β-*D*-glucopyranosyl)-2″-naphthalene]-propionyl-7-azanorbornane* (**8**). A mixture of 4 ml of acetic anhydride–

pyridine (1:1) was added to amide **6** (20 mg, 0.042 mmol). The reaction mixture was stirred for 6 h. The reaction was worked up by addition of 10 ml of water and extraction with dichloromethane. The organic layer was washed with water and dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel. Elution with 25% of hexane in ethyl acetate gave compound **8** as a clear oil (25 mg, 98% yield). ^{1}H NMR ($CDCl_3$): δ 7.69 (3H, m), 7.44 (1H, dd, J = 8.6, 1.5 Hz), 7.30 (1H, d, J = 2.5 Hz), 7.16 (1H, dd, J = 9.0 Hz, 2.5), 5.29 (1H, dd, J = 9.1, 9.1 Hz), 5.24–5.16 (2H, m), 4.69 (1H, bs), 4.45 (1H, dd, J = 11.9, 2.3 Hz), 4.30 (1H, dd, J = 11.9, 5.8 Hz), 4.19 (1H, bs), 3.90 (1H, q, J = 7.0 Hz), 3.78 (1H, ddd, J = 9.9, 5.8, 2.3 Hz), 3.48 (1H, dd, J = 9.4, 9.4 Hz), 3.47 (3H, s), 2.12 (3H, s), 2.09 (3H, s), 2.06 (3H, s), 1.78 (2H, bs), 1.60–1.24 (4H, m), 1.50 (3H, d, J = 6.9 Hz), 1.12 (1H, m), 0.83 (1H, m); ^{1}H NMR (CD_3OD): δ 7.75 (3H, m), 7.43 (1H, dd, J = 8.5, 1.8 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.16 (1H, dd, J = 9.0, 2.4 Hz), 5.36 (1H, d, J = 8.5 Hz), 5.33 (1H, dd, J = 9.2, 9.2 Hz), 5.12 (1H, dd, J = 9.6, 8.0 Hz), 4.56 (1H, t, J = 4.7 Hz), 4.43 (1H, dd, J = 12.1, 2.2 Hz), 4.37 (1H, t, J = 4.5 Hz), 4.29 (1H, dd, J = 12.1, 5.9 Hz), 4.08 (1H, q, J = 6.7 Hz), 3.92 (1H, ddd, J = 10.0, 6.0, 2.2 Hz), 3.51 (1H, dd, J = 9.5, 9.5 Hz), 3.47 (3H, s), 2.09 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.84 (1H, m), 1.73 (1H, m), 1.53–1.40 (3H, m), 1.45 (3H, d, J = 6.8 Hz), 1.33 (1H, m), 1.18 (1H, m), 0.84 (1H, m); ^{13}C NMR ($CDCl_3$): δ 170.8 (CO), 170.2 (CO), 169.9 (CO), 169.8 (CO), 154.8 (C), 138.9 (C), 133.2 (C), 130.4 (C), 129.5 (CH), 127.8 (CH), 126.6 (CH), 125.6 (CH), 119.3 (CH), 111.5 (CH), 99.2 (CH), 77.9 (CH), 75.0 (CH), 73.3 (CH), 71.2 (CH), 63.0 (CH_2), 60.6 (CH_3), 56.0 (CH), 53.4 (CH), 44.9 (CH), 31.0 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.2 (CH_3); ^{13}C NMR (CD_3OD): δ 172.5 (CO), 172.0 (CO), 171.8 (CO), 171.5 (CO), 156.2 (C), 139.8 (C), 134.8 (C), 131.7 (C), 130.6 (C), 129.0 (CH), 127.4 (CH), 126.9 (CH), 120.2 (CH), 112.3 (CH), 99.7 (CH), 79.2 (CH), 76.3 (CH), 74.4 (CH), 73.4 (CH), 64.1 (CH_2), 60.8 (CH_3), 57.6 (CH), 55.0 (CH), 45.5 (CH), 31.6 (CH_2), 30.7 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.2 (CH_3).

N-(o-Anisoyl)-7-azanorbornane (**9a**). A solution of 7-azanorbornane hydrochloride (239 mg, 2 mmol) and triethylamine (304 mg, 3 mmol) in 8 ml of dichloromethane, was treated with *o*-anisoyl chloride (426.5 mg, 2.5 mmol) in 2 ml of dichloromethane. The mixture was stirred at 0 °C for 6 h. The reaction was quenched with 10 ml of water, and the product was extracted with dichloromethane. The organic layer was washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using 40% ethyl acetate in hexanes to give compound **9a** as a white solid (453 mg, 98% yield). TLC: R_f = 0.24 (3:2, ethyl acetate/hexane); mp 88–89 °C; ^{1}H NMR ($CDCl_3$): δ 7.34 (1H, ddd, J = 8.4, 7.5, 1.7 Hz), 7.29 (1H, dd, J = 7.5, 1.7 Hz), 6.96 (1H, dt, J = 7.5, 1.7 Hz), 6.92 (1H, d, J = 8.3 Hz), 4.81 (1H, t, J = 4.8 Hz), 3.83 (3H, s), 3.73 (1H, t, J = 4.8 Hz), 1.93 (2H, m), 1.77 (2H, m), 1.55–1.38 (4H, m); ^{13}C NMR ($CDCl_3$): δ 164.5 (CO), 155.7 (C), 130.4 (CH), 128.2 (CH), 126.5 (C). 120.6 (CH), 111.1 (CH), 57.5 (CH), 55.5 (CH_3), 52.8 (CH), 30.4 ($2CH_2$), 29.3 ($2CH_2$); IR (film): 2947, 1621, 1599, 1460, 1242.

N-(m-Anisoyl)-7-azanorbornane (**9b**). A solution of 7-azanorbornane hydrochloride (239 mg, 2 mmol) and triethylamine (304 mg, 3 mmol) in 8 ml of dichloromethane, was treated with *m*-anisoyl chloride (426.5 mg, 2.5 mmol) in 2 ml of dichloromethane. The mixture was stirred at 0 °C for 6 h. The reaction was quenched with 10 ml of water, and the product was extracted with dichloromethane. The organic layer was washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using 35% ethyl acetate in hexanes to give compound **9b** as a white solid (458 mg, 99% yield). TLC: R_f = 0.28 (7:3, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.30 (1H, dd, J = 8.0, 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.09 (1H, s), 6.98 (1H, dd, J = 8.0, 2.0 Hz), 4.74 (1H, bs), 4.15 (1H, bs), 3.83 (3H, s), 1.91 (2H, bs), 1.82 (2H, bs), 1.49 (4H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$): δ 168.4 (CO), 159.5 (C), 137.6 (C), 129.3 (CH), 119.9 (CH), 116.3 (CH), 113.0 (CH), 58.8 (CH), 55.4 (CH_3), 53.7 (CH), 30.5 ($2CH_2$), 28.8 ($2CH_2$); IR (film): 2952, 1633, 1580, 1455, 1249; HRMS: Calculated for $C_{14}H_{17}NO_2 + H^+$: 232.1337. Found: 232.1335.

N-(p-Anisoyl)-7-azanorbornane (**9c**). A solution of 7-azanorbornane hydrochloride (239 mg, 2 mmol) and triethylamine (304 mg, 3 mmol) in 16 ml of dichloromethane, was treated with *p*-anisoyl chloride (426.5 mg, 2.5 mmol) in 4 ml of dichloromethane. The mixture was stirred at 0 °C for 6 h. The reaction was quenched with 10 ml of water, and the product was extracted with dichloromethane. The organic layer was washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using 40% ethyl acetate in hexanes to give compound **9c** as a clear oil (435 mg, 94% yield). TLC: $R_f = 0.37$ (1:1, hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.55 (2H, d, $J = 8.8$ Hz), 6.90 (2H, d, $J = 8.8$ Hz), 4.68 (1H, bs), 4.20 (1H, bs), 3.84 (3H, s), 1.86 (4H, bs), 1.50 (2H, bs), 1.47 (2H, bs); ^{13}C NMR ($CDCl_3$): δ 168.9 (CO), 161.5 (C), 129.9 (2CH), 128.6 (C), 113.5 (2CH), 59.0 (CH), 55.5 (CH_3), 54.1 (CH), 30.5 ($2CH_2$), 28.9 ($2CH_2$); IR (film): 2952, 1607, 1388, 1253; HRMS: Calculated for $C_{14}H_{17}NO_2 + H^+$: 232.1337. Found: 232.1339.

N-[o-Anisoyl]-7-aza-2-endo-norbornanol (**10a**). TLC: $R_f = 0.31$ (9:1, dichloromethane/methanol); $[\alpha] = +3.6$ (*c* 1.0, $CHCl_3$); mixture of rotamers: ^{1}H NMR ($CDCl_3$): δ 7.34 (2H, ddd, $J = 8.3$, 7.4, 1.8 Hz), 7.24 (2H, dd, $J = 7.4$, 1.8 Hz), 6.95 (2H, ddd, $J = 7.4$, 7.4, 0.6 Hz), 6.90 (2H, dd, $J = 8.3$, 0.6 Hz), 4.66 (2H, dd, $J = 9.8$, 5.1 Hz), 4.39 (1H, m), 4.24 (1H, m), 3.81 (3H, s), 3.80 (3H, s), 3.64 (1H, dd, $J = 4.7$, 4.7 Hz), 3.60 (1H, dd, $J = 4.7$, 4.7 Hz), 3.42 (1H, bs), 3.18 (1H, bs), 2.27 (2H, m), 2.16 (2H, m), 1.90 (1H, m), 1.74 (2H, m), 1.56 (3H, m), 1.11 (2H, ddd, $J = 16$, 12.5, 3.5 Hz); ^{13}C NMR ($CDCl_3$): δ 165.1 (2CO), 155.8 (2C), 130.8 (2CH), 128.5 (CH), 128.4 (CH), 126.0 (C), 125.8 (C) 120.8 (2CH), 111.3 (CH), 111.2 (CH), 70.9 (CH), 70.0 (CH), 61.5 (CH), 59.0 (CH), 57.2 (CH), 55.7 ($2CH_3$), 54.4 (CH), 39.8 (CH_2), 38.9 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 21.6 (CH_2), 20.4 (CH_2); IR (film): 3365, 2951, 1608, 1469, 1249; HRMS: Calculated for $C_{14}H_{17}NO_3 + H^+$: 248.1287. Found: 248.1288.

N-[m-Anisoyl]-7-aza-2-endo-norbornanol (**10b**). Mixture of rotamers: ^{1}H NMR ($CDCl_3$): δ 7.30 (2H, dd, $J = 8.1$, 8.1 Hz), 7.07 (2H, d, $J = 8.1$ Hz), 7.06 (2H, s), 6.98 (2H, ddd, $J = 8.3$, 2.8, 0.9 Hz), 4.66 (2H, bs), 4.47 (1H, bs), 4.35 (1H, bs), 4.09 (2H, bs), 3.83 (6H, s), 2.44 (4H, bs), 1.90 (2H, m), 1.78 (4H, bs), 1.61 (2H, m), 1.17 (2H, dd, $J = 12.7$, 3.4 Hz); ^{13}C NMR (CD_3OD): δ 170.6 (2CO), 161.3 (2C), 137.9 (2C), 130.9 (2CH), 120.7 (2CH), 117.7 (2CH), 114.1 (2CH), 71.5 (CH), 70.5 (CH), 64.2 (CH), 61.7 (CH), 59.4 (CH), 56.6 (CH), 56.0 ($2CH_3$), 40.4 (CH_2), 38.9 (CH_2), 31.5 (CH_2), 29.9 (CH_2), 22.5 (CH_2), 20.8 (CH_2).

N-[p-Anisoyl]-7-aza-2-endo-norbornanol (**10c**). TLC: $R_f = 0.41$ (9:1, dichloromethane/methanol); $[\alpha] = -4.2$ (*c* 1.0, $CHCl_3$); mixture of rotamers: ^{1}H NMR (CD_3OD): δ 7.50 (4H, d, $J = 8.6$ Hz), 6.97 (4H, d, $J = 8.6$ Hz), 4.52 (2H, bs), 4.30 (2H, bs), 4.14 (2H, bs), 4.07 (2H, bs), 3.83 (6H, s), 2.31–2.20 (4H, m), 1.83 (2H, bs), 1.74–1.52 (4H, m), 1.16 (2H, dd, $J = 12.7$, 3.4 Hz); ^{13}C NMR (CD_3OD): δ 170.9 (2CO), 163.4 (2C), 130.7 (4CH), 128.4 (C), 114.8 (4CH), 71.4 (CH), 70.3 (CH), 64.5 (CH), 61.9 (CH), 59.4 (CH), 56.6 (CH), 55.9 ($2CH_3$), 40.2 (CH_2), 38.7 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 22.2 (CH_2), 20.6 (CH_2); IR (film): 3383, 3007, 1608, 1435, 1255, 756.

N-[o-Hydroxyl-p-(4″-O-Methyl-β-D-glucopyranosyl)benzoyl]-7-azanorbornane (**11a**). TLC: $R_f = 0.26$ (9:1, dichloromethane/methanol); mp 136–137 °C; $[\alpha] = -45.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD): δ 7.08 (1H, dd, $J = 8.6$, 2.8 Hz), 7.04 (1H, d, $J = 2.8$ Hz), 6.80 (1H, dd, $J = 8.6$ Hz), 4.74 (1H, d, $J = 7.8$ Hz), 4.36 (2H, bs), 3.82 (1H, dd, $J = 12.1$, 1.4 Hz), 3.69 (1H, dd, $J = 12.1$, 4.7 Hz), 3.57 (3H, s), 3.54 (1H, dd, $J = 9.2$, 9.2 Hz), 3.41 (1H, dd, $J = 9.2$, 7.8 Hz), 3.36 (1H, m), 3.17 (1H, dd, $J = 9.2$, 9.2 Hz), 1.87 (4H, s), 1.55 (4H, s); ^{13}C NMR (CD_3OD): δ 167.5 (CO), 152.2 (C), 151.6 (C), 123.0 (C), 122.2 (CH), 118.1 (2CH), 103.3 (C), 80.6 (CH), 77.9 (CH), 77.1 (CH), 75.0 (CH), 62.1 (CH_2), 60.9 (CH_3), 57.3 (2CH), 30.4 ($4CH_2$); IR (film): 3427, 2953, 1579, 1482, 1067. EIMS 410 ($M + H^+$, 100), 233 (61), 127 (69).

N-[m-(4″-O-Methyl-β-D-glucopyranosyl)benzoyl]-7-azanorbornane (**11b**). TLC: $R_f = 0.27$ (9:1, dichloromethane/methanol); $[\alpha] = -34.3$ (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.28 (1H, dd, $J = 7.8$, 7.8 Hz), 7.23 (1H, bs), 7.13 (1H, d, $J = 7.5$ Hz), 7.08 (1H, dd, $J = 8.1$, 2.2 Hz), 4.89 (1H, d, $J = 7.8$ Hz), 4.70 (1H, bs), 4.57 (1H, bs), 4.27 (1H, bs), 4.12 (1H, bs), 3.84 (1H, d, $J = 12.0$ Hz), 3.68 (1H, dd, $J = 12.0$, 4.8 Hz), 3.61 (1H, dd, $J = 8.8$, 8.8 Hz), 3.55 (1H, dd, $J = 8.2$, 8.2 Hz), 3.52 (3H, s), 3.38

(1H, m), 3.18 (1H, dd, J = 9.0, 9.0 Hz), 3.00 (1H, bs), 1.94–1.70 (4H, m), 1.48 (4H, m); ^{13}C NMR ($CDCl_3$): δ 167.9 (CO), 157.2 (CH), 137.4 (C), 129.6 (C), 121.8 (CH), 119.0 (CH), 116.2 (CH), 100.5 (CH), 79.0 (CH), 76.6 (CH), 75.8 (CH), 73.7 (CH), 61.8 (CH_2), 60.8 (CH_3), 58.9 (CH), 54.1 (CH), 30.5 ($2CH_2$), 28.9 ($2CH_2$).

*N-[p-(4″-O-Methyl-β-*D*-glucopyranosyl)benzoyl]-7-azanorbornane* (**11c**). TLC: R_f = 0.27 (9:1, dichloromethane/methanol); ^{1}H NMR ($CDCl_3$): δ 7.47 (1H, d, J = 8.7 Hz), 6.98 (1H, d, J = 8.7 Hz), 4.88 (1H, d, J = 7.8 Hz), 4.69 (1H, bs), 4.40–3.40 (3H, bs), 4.12 (1H, m), 3.86 (1H, d, J = 12.0 Hz), 3.68 (1H, dd, J = 12.0, 4.8 Hz), 3.59 (1H, dd, J = 8.8, 8.8 Hz), 3.55 (1H, m), 3.53 (3H, s), 3.37 (1H, d, J = 10.2 Hz), 3.16 (1H, dd, J = 9.2, 9.2 Hz), 1.92–1.70 (4H, m), 1.47 (4H, m); ^{13}C NMR ($CDCl_3$): δ 168.4 (CO), 159.0 (C), 130.1 (C), 129.8 (2CH), 116.3 (2CH), 100.1 (CH), 79.1 (CH), 76.6 (CH), 75.8 (CH), 73.7 (CH), 61.8 (CH_2), 60.8 (CH_3), 58.9 (CH), 54.1 (CH), 30.5 ($2CH_2$), 28.8 ($2CH_2$).

N-(p-Hydroxybenzoyl)-7-azanorbornane (**12c**), mp 17 °C; ^{1}H NMR ($CDCl_3$): δ 7.40 (2H, d, J = 8.7 Hz), 6.80 (2H, d, J = 8.7 Hz), 4.71 (1H, bs), 4.35 (1H, bs), 4.23 (1H, bs), 2.26 (1H, m), 1.86 (4H, m), 1.49 (4H, m); ^{13}C NMR ($CDCl_3$): δ 169.2 (C), 159.7 (C), 129.9 (2CH), 126.6 (C), 115.5 (2CH), 59.4 (CH), 54.3 (CH), 30.5 ($2CH_2$), 28.9 ($2CH_2$); IR (film): 3030, 2958, 2875, 1602, 1569, 1433.

N-(o-Methoxyphenyl-methyl)-7-aza-2-endo-norbornanol (**13a**). ^{1}H NMR ($CDCl_3$): δ 7.46 (1H, d, J = 7.4 Hz), 7.21 (1H, dt, J = 8.2, 1.7 Hz), 6.94 (1H, dt, J = 7.4, 1.7 Hz), 6.84 (1H, d, J = 8.2 Hz), 4.37 (1H, m), 3.81 (3H, s), 3.63 (1H, d, J = 14.6 Hz), 3.56 (1H, d, J = 14.6 Hz), 3.32 (1H, t, J = 4.6 Hz), 3.27 (1H, t, J = 4.8 Hz), 2.76 (1H, bs), 2.24 (1H, m), 2.11 (1H, ddd, J = 12.7, 9.4, 4.6 Hz), 1.97 (1H, m), 1.76 (1H, m), 1.48 (1H, ddd, J = 12.2, 9.4, 4.1 Hz), 0.94 (1H, dd, J = 12.4, 3.2 Hz); ^{13}C NMR ($CDCl_3$): δ 157.4 (C), 129.6 (CH), 128.3 (C), 127.8 (CH), 120.7 (CH), 110.2 (CH), 71.4 (CH), 64.8 (CH), 61.5 (CH), 55.4 (CH_3), 45.6 (CH_2), 40.1 (CH_2), 27.7 (CH_2), 18.8 (CH_2).

N-(m-Methoxyphenyl-methyl)-7-aza-2-endo-norbornanol (**13b**). ^{1}H NMR ($CDCl_3$): δ 7.22 (1H, dd, J = 7.8, 7.8 Hz), 6.92 (2H, m), 6.79 (1H, ddd, J = 8.3, 2.6, 0.9 Hz), 4.33 (1H, m), 3.80 (3H, s), 3.58 (1H, d, J = 13.1 Hz), 3.54 (1H, d, J = 13.1 Hz), 3.28 (1H, t, J = 4.6 Hz), 3.23 (1H, t, J = 4.8 Hz), 2.52 (1H, bs), 2.21 (1H, m), 2.09 (1H, ddd, J = 12.7, 9.4, 4.5 Hz), 1.93 (1H, m), 1.72 (1H, m), 1.49 (1H, ddd, J = 12.3, 9.5, 4.2 Hz), 0.93 (1H, dd, J = 12.4, 3.4 Hz); ^{13}C NMR ($CDCl_3$): δ 159.8 (C), 141.5 (C), 129.3 (CH), 121.0 (CH), 114.3 (CH), 112.4 (CH), 71.5 (CH), 64.1 (CH), 60.9 (CH), 55.4 (CH_3), 52.1 (CH_2), 40.5 (CH_2), 27.5 (CH_2), 18.6 (CH_2).

N-(p-Methoxyphenyl-methyl)-7-aza-2-endo-norbornanol (**13c**). TLC: R_f = 0.49 (89:10:1, dichloromethane/methanol/ammonium hydroxide); ^{1}H NMR ($CDCl_3$): δ 7.26 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 4.31 (1H, m), 3.80 (3H, s), 3.53 (1H, d, J = 13.0 Hz), 3.49 (1H, d, J = 13.0 Hz), 3.25 (1H, t, J = 4.6 Hz), 3.21 (1H, t, J = 5.0 Hz), 2.19 (1H, m), 2.09 (1H, ddd, J = 13.1, 9.5, 4.5 Hz), 1.92 (1H, m), 1.87 (1H, bs), 1.72 (1H, m), 1.48 (1H, ddd, J = 12.4, 9.5, 4.2 Hz), 0.92 (1H, dd, J = 12.5, 3.3 Hz); ^{13}C NMR ($CDCl_3$): δ 158.8 (C), 131.9 (C), 129.9 (2CH), 113.8 (2CH), 71.5 (CH), 63.9 (CH), 60.6 (CH), 55.4 (CH_3), 51.5 (CH_2), 40.0 (CH_2), 27.4 (CH_2), 18.5 (CH_2).

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