Synthesis of an Immunogenic Template for the Generation of Catalytic Antibodies for (−)-Cocaine Hydrolysis

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Introduction

Abuse of (−)-cocaine has become a major public health problem in the United States. The relative risk to individuals and the cost to society is difficult to estimate but the burden to the United States is large in terms of economic and personal loss. In fact, (−)-cocaine abuse is one of the most common causes for emergency room visits in United States hospitals, especially in the inner cities.

The pharmacotherapies to combat (−)-cocaine abuse that have been attempted thus far have not been successful. Consequently, there has been a great interest in developing novel therapeutic strategies, particularly those derived from immunological sources for combating health problems arising from (−)-cocaine abuse.[1,2] Landry and co-workers attempted to procure catalytic antibodies specific for (−)-cocaine hydrolysis, and although antibodies were isolated, their activity was reportedly quite low.[1] In that study, the ester hapten **1** was coupled to a carrier protein and used for immunization (Figure 1). Although **1** possessed the C3 phosphonate functionality commonly used for mimicking the transition state of benzoyl ester hydrolysis, it is possible that the ester linkage at the C2 position was metabolically prone to hydrolysis *in vivo* and thus decreased its immunogenic lifetime. As a consequence of a decreased residence time of the hapten in the immunized animal, the potential for an appropriate immune response was possibly reduced. For example, it is known that aliphatic C2-esters of (−)-cocaine are extensively hydrolyzed by serum and hepatic microsomal esterases from animals and humans.[3] Therefore, to circumvent such potential shortcomings, we designed and synthesized an analogous hapten (**2**) with a more metabolically stable linkage at the C2 position (i.e., an amide) in order to procure antibodies with more catalytic activity for (−)-cocaine hydrolysis. This report will describe the successful synthesis of phosphonate **2**. The novel strategy utilized in our study was to avoid the difficulties associated with (−)-cocaine's unique chemistry by synthesizing the phosphonate **2** through an N-8-amino protection strategy.

Results and Discussion

The preparation of (−)-cocaine analogues, where either the C2 or C3 functional groups were altered, has generally relied on simple and efficient functional group transformations.[4,5] Such modifications have not required special consideration of the bridgehead nitrogen for

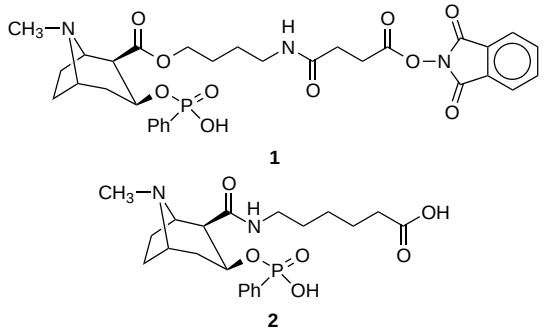
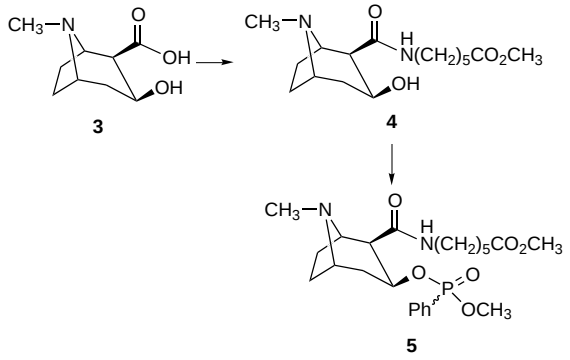


Figure 1.

Scheme 1



acceptable synthetic results. Therefore, the initial strategy for the synthesis of **2** envisioned a straightforward amidation of ecgonine (**3**) followed by phosphonylation (Scheme 1). Although treatment of ecgonine (**3**) with oxalyl chloride followed by reaction with methyl 6-aminocaproate generated amide **4**, attempts at efficient phosphonylation of **4** under various conditions were unsuccessful.

The bridgehead N-8 nitrogen, in addition to steric hindrance induced by the alkyl amide at C2, may contribute to the lack of reactivity toward phosphonylating reagents by possible electronic interactions. It was anticipated that protection of the nitrogen would circumvent the first of these problems (Scheme 2). This type of strategy has been recently employed in the preparation of the tropane alkaloid ferruginine.[6] Therefore, *N*-norcocaine (**6**) was fully hydrolyzed to *N*-norecgonine in an analogous fashion to (−)-cocaine being hydrolyzed to ecgonine[7] and subsequently N-protected with benzyl chloroformate (CBZ-Cl) to give the hydroxy acid **7**. Coupling of **7** with methyl 6-aminocaproate in the presence of DCC provided the alcohol **8**. Phosphonylation of **8** was carried out by the method described by Zhao and Landry[8] (i.e., tetrazole catalysis) to afford the phenylphosphonate **9** in an acceptable overall yield of 23% from *N*-norcocaine. In contrast to the 15 h phosphonylation protocol for secondary alcohols by Zhao and Landry,[8] it is noteworthy that a decrease of the reaction time for phosphonylation to 1 h increased the yield of **9**

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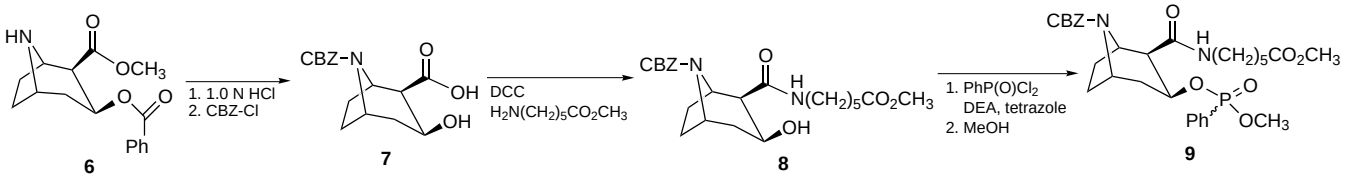
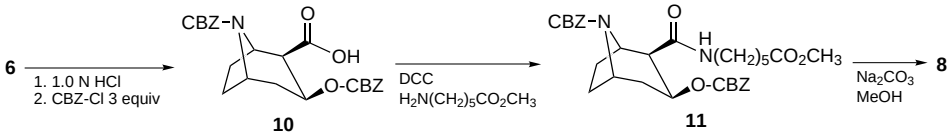
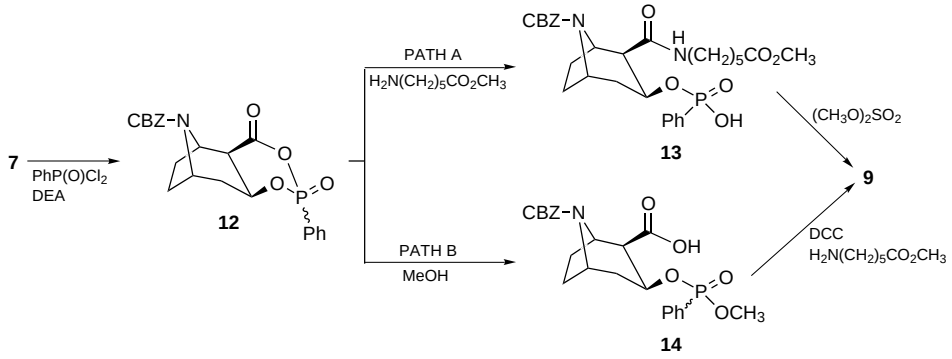
Scheme 2



Scheme 3



Scheme 4



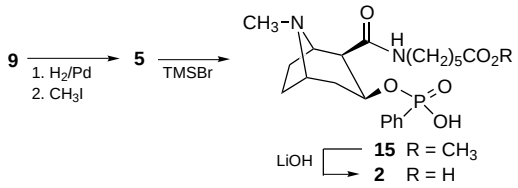
from 25% to nearly 60%. Although **9** existed as a mixture of isomers (presumably diastereomeric at phosphorus) identified by ^{31}P and ^{1}H NMR, mass spectral and elemental analysis of **9** were consistent with the expected product. Separation of these isomers was not necessary because the ultimate synthesis of **15** or **2** (i.e., after dealkylation) would result in the loss of chirality at phosphorus.

It is important to note that the reaction of *N*-norecgonine with excess CBZ-Cl (Scheme 3) led to the bis-*N*,*O*-CBZ-protected carboxylic acid **10**. Although unstable, the bis-*N*,*O*-CBZ-protected carboxylic acid **10** was successfully coupled with methyl 6-aminocaproate to form amide **11**. Additionally, we found that amide **11** could be selectively O-deprotected to give alcohol **8**.

An alternative route to **9** was developed taking advantage of the favorable proximity and configuration of the C2 carboxylic acid and C3 alcohol. As shown in Scheme 4, this reaction sequence involved a cyclic mixed anhydride. The precedent for this synthetic approach is based on the regioselective formation of amides from carbon−phosphorus mixed anhydrides when reacted with amines.[9] Thus, reaction of the hydroxy acid **7** with phenylphosphonic dichloride followed by ring-opening amidation with methyl 6-aminocaproate provided the amide phosphonate **13** in good yield (Scheme 4, path A) and subsequent methylation afforded the methyl phosphonate **9**. As expected, the opposite regioselectivity was observed when the cyclic intermediate was intercepted with methanol to produce the corresponding methyl phosphonate **14** (Scheme 4, path B). Coupling of **14** with methy 6-aminocaproate in the presence of DCC also provided **9**.

To obtain the desired final product **2** from **9**, a sequence of simple transformations was executed (Scheme 5).

Scheme 5



Deprotection of **9** via catalytic hydrogenolysis followed by methylation afforded the *N*-methyl product **5**. Dealkylation of the methyl phosphonate **5** was readily accomplished with trimethylsilyl bromide[10] (TMSBr) to form the phosphonic acid **15**. The hydrolysis of the methyl ester of **15** was achieved with LiOH to give the final hapten **2** as the dilithium salt. Although combustion analysis of **2** as the dilithium salt gave accurate results for hydrogen and nitrogen, an acceptable result for carbon was not feasible due to interference with lithium. However, ^{1}H and ^{31}P NMR as well as mass spectral analysis were consistent with the desired product.

In conclusion, synthetic difficulties in phosphonylation of the C3 position of ecgonine-related materials were circumvented by protection of the N-8 bridgehead nitrogen. In addition, use of the UV-active CBZ protecting group facilitated chromatographic isolation of the ecgonine derivatives described herein. A parallel synthetic strategy utilizing the favorable proximity and configurations of the C2 carboxylic acid and the C3 hydroxyl of *N*-norecgonine to form a reactive cyclic carboxylic-phosphonic mixed anhydride was explored. It was discovered that both routes were viable and gave similar overall yields. The synthesized hapten **2** has now been coupled to an immunogenic protein, and results regarding the

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procurement of catalytic antibodies utilizing hapten **2** will be forthcoming.

Experimental Section

General Procdures. All solvents used in reactions were distilled prior to use. All other reagents were used as supplied unless otherwise stated. Ecgonine and *N*-norcocaine were obtained from NIDA. All chromatography was performed with silica gel unless specified otherwise. ^{1}H and ^{31}P NMR spectra were recorded on a Varian VXR 300. ^{1}H NMR chemical shifts are relative to TMS (δ = 0.00 ppm) or $CDCl_3$ (δ = 7.24 ppm). ^{31}P NMR chemical shifts are relative to H_3PO_4 (δ = 0.00 ppm).

3β-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2β-carboxylic Acid *N*-(5-Carbomethoxypentyl)amide (4). To a stirred suspension of ecgonine·HCl (1.0 g, 4.51 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added pyridine (0.365 mL, 4.51 mmol) followed by oxalyl chloride (1.57 mL, 18.04 mmol). The reaction was allowed to warm to room temperature for 3 h, at which time the solution became pale pink in color. The solvent was evaporated and dried overnight *in vacuo* at room temperature to give the crude acid chloride of ecgonine. A solution of methyl 6-aminocaproate (1.23 g, 6.76 mmol) and pyridine (1.46 mL, 18.04 mmol) in CH_2Cl_2 was added to the crude ecgonine acid chloride at 0 °C and the reaction was allowed to stir for 1 h. The mixture was treated with Na_2CO_3 (10% w/v) and extracted twice with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$, and the solvent was evaporated *in vacuo* overnight to remove excess pyridine. The crude mixture was purified by flash silica chromatography (MeOH:$CHCl_3$, 25:75; R_f = 0.15) to give the product as a pale yellow semisolid (0.788 g, 56% yield). ^{1}H NMR ($CDCl_3$): δ 1.31−1.39 m, 2H; 1.48−1.55 m, 3H; 1.58−1.65 m, 2H; 1.76 dd, 1H, J = 4.1, 19.2; 1.86 t, 1H, J = 9.3; 2.13 t, 2H, J = 7.4; 2.33 s, 3H; 2.56 d, 1H, J = 16.8; 3.22 s, 1H; 3.28 q, 2H, J = 6.9; 3.64 s, 3H; 3.68 d, 1H, J = 5.3; 5.71 s, 1H br; 6.23 s, 1H. MS (FAB): m/z 313 (M + H).

8-(Benzyloxycarbonyl)-3β-hydroxy-8-azabicyclo[3.2.1]-octane-2β-carboxylic Acid (7). *N*-Norcocaine (**6**) (0.5 g, 1.73 mmol) was dissolved in 0.8 N HCl (10 mL) and refluxed overnight to generate *N*-norecgonine. The solution was allowed to cool to room temperature and extracted with diethyl ether (20 mL) to remove benzoic acid. The aqueous layer was treated with Na_2CO_3 (solid) to adjust the pH to 10. Benzyl chloroformate (0.271 mL, 1.90 mmol) was added to the aqueous solution and stirred at room temperature for 3 h. Ethyl acetate (15 mL) was added to the reaction mixture followed by the addition of HCl (concd) to adjust the pH to 2. The aqueous layer was extracted once with ethyl acetate and twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to a yellow oil. The crude mixture was purified by flash silica gel chromatography (MeOH:CH_2Cl_2 10:90, v:v; R_f = 0.25) to give **7** as a pale yellow oil (0.235 g, 44% yield). ^{1}H NMR ($CDCl_3$): δ 1.64−1.67 m, 2H; 1.88−1.97 m, 2H; 1.99−2.09 m, 2H; 2.96 s, 1H; 4.04−4.08 m, 1H; 4.44 s, 1H; 4.86 s, 1H; 5.12 s, 2H; 7.33 s, 5H.

8-(Benzyloxycarbonyl)-3β-hydroxy-8-azabicyclo[3.2.1]-octane-2β-carboxylic Acid *N*-(5-Carbomethoxypentyl)-amide (8). From 7. N-CBZ-norecgonine (**7**) (0.249 g, 0.86 mmol) was dissolved in CH_2Cl_2 (8 mL) at room temperature followed by the addition of DCC (0.185 g, 0.898 mmol). The mixture was stirred for 10 min, after which a white precipitate formed. 6-Aminocaproic acid methyl ester hydrochloride (0.178 g, 0.980 mmol) along with TEA (0.137 mL, 0.980 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to the above reaction mixture. The mixture was allowed to stir overnight at room temperature, after which it was filtered twice. The filtrate was concentrated *in vacuo* and purified by flash silica gel chromatography (ethyl acetate; R_f = 0.3) to give the desired product as a colorless oil (0.281 g, 80% yield). ^{1}H NMR ($CDCl_3$): δ 1.23−1.33 m, 2H; 1.39−1.41 m, 2H; 1.57−1.74 m, 5H; 1.89−2.04 m, 3H; 2.29 t, 2H J = 7.4; 2.74 s, 1H; 3.15−3.17 m, 2H; 3.66 s, 3H; 4.11−4.13 m, 1H; 4.49 s, 1H; 4.65 s, 1H; 5.11 s, 2H; 7.33 s, 5H. **From 11.** Amide **11** (0.020 g, 0.035 mmol) was dissolved in MeOH (2 mL) at room temperature, Na_2CO_3 (0.015 g, 0.142 mmol) was added, and the reaction was allowed to stir until complete consumption of starting material was observed by TLC (3 h). The solvent was evaporated *in vacuo*, and the product was purified by preparative TLC (hexane:ethyl acetate, 1:2 v:v; R_f = 0.12) to give a colorless oil (0.0125 g, 82% yeild). Spectral data were identical to that described above.

3β-((Benzyloxycarbonyl)oxy)-8-(benzyloxycarbonyl)-8-azabicyclo[3.2.1]octane-2β-carboxylic Acid *N*-(5-Carbomethoxypentyl)amide (11). *N*-Norcocaine (**6**) (0.289 g, 1.0 mmol) was dissolved in 0.8 N HCl (10 mL) and refluxed overnight to generate *N*-norecgonine. The solution was allowed to cool to room temperature and extracted with diethyl ether (20 mL) to remove benzoic acid. The aqueous layer was treated with Na_2CO_3 (solid) to adjust the pH to 10. Benzyl chloroformate (0.428 mL, 3.0 mmol) was added to the aqueous solution and stirred at room temperature for 3 h. Ethyl acetate (15 mL) was added to the reaction mixture followed by the addition of HCl (concd) to adjust the pH to 2. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude mixture was purified by flash silica gel chromatography (hexane:ethyl acetate, 2:1, v:v; R_f = 0.15) to give **10** as a pale yellow oil. The bis-*O*,*N*-CBZ-carboxylic acid **10** was observed to decompose readily and was therefore used immediately in the subsequent reaction. The carboxylic acid **10** (0.054 g, 0.123 mmol) was dissolved in CH_2Cl_2 (1.5 mL) at room temperature, followed by the addition of TEA (0.021 mL, 0.147 mmol) and methyl 6-aminocaproate (0.027 g, 0.147 mmol). DCC was dissolved in CH_2Cl_2 (0.5 mL), added to the reaction mixture, and allowed to stir overnight. The reaction was filtered twice, concentrated to an oil, and purified by flash chromatography (hexane:ethyl acetate, 1:1 v:v; R_f = 0.12) to give the product as a clear oil (0.022 g, 31% yeild). ^{1}H NMR ($CDCl_3$): δ 1.24 q, 2H, J = 7.2; 1.34 q, 2H, J = 7.3; 1.53 m, 2H; 1.68 d, 2H, J = 7.3; 1.88−2.02 m, 3H; 2.23 t, 2H, J = 7.5; 2.36 dt, 1H, J = 2.9, 12.2; 2.85 d, 1H, J = 6.8; 3.05−3.14 m, 2H; 3.63 s, 1H; 4.52 s, 1H; 4.65 d, 1H, J = 6.6; 4.99−5.14 m, 5H; 5.83 s, 1H; 7.27−7.34 m, 10H. MS (FAB): m/z 567 (M + H).

8-(Benzyloxycarbonyl)-3β-(methoxyphenylphosphinyl)-8-azabicyclo[3.2.1]octane-2β-carboxylic Acid *N*-(5-Carbomethoxypentyl)amide (9). From 8. Tetrazole (0.0021 g 0.03 mmol) and **8** (0.141 g, 0.326 mmol) were dissolved in benzene and stirred under $Ar_{(g)}$ at 4 °C. *N*,*N*-Diisopropylethylamine (0.13 mL, 0.730 mmol) was added via syringe followed by the addition of phenylphosphonic dichloride (0.048 mL, 0.338 mmol). The reaction was allowed to warm to room temperature for 1 h, followed by the dropwise addition of methanol (0.040 mL, 0.905 mmol), and the mixture was allowed to stir an additional 30 min. The solvent was removed *in vacuo*, and the product was purified by flash chromatography (MeOH:ethyl acetate 5:95 v:v, R_f = 0.2) to give a colorless oil (0.110 g, 58% yield). ^{1}H NMR ($CDCl_3$): δ 1.14−1.74 m, 8H; 1.80−2.05 m, 3H; 2.14−2.31 m, 2H; 2.55 ddt, 1H, J = 48.0, 12.1, 2.6; 2.77 ddd, 1H, J = 48.6, 6.5, 2.0; 2.91−3.10 m, 2H; 3.61−3.68 m, 6H; 4.37−4.45 m, 1H; 4.60 d, 1H, J = 6.1; 4.64−4.82 m, 1H; 5.06 d, 2H, J = 5.4; 5.89 dt, 1H, J = 73.0, 5.3; 7.25−7.33 m, 5H; 7.37−7.58 m, 3H; 7.74 dd, 2H, J = 13.6, 6.9. ^{31}P NMR: δ 20.67, 21.01. MS (FAB): m/z 587 (M + H) Anal. Calcd for $C_{16}H_{19}NO_5$: C, 60.62; H, 6.84; N, 4.88. Found: C, 60.95; H, 6.77; N, 4.81. **From 12, Path A.** A benzene (3 mL) solution of N-CBZ-norecgonine (**7**) (100 mg, 0.33 mmol), diisopropylamine (0.23 mL, 1.32 mmol), and tetrazole (2 mg, 0.03 mmol) under $Ar_{(g)}$ was cooled to 5 °C and treated with phenylphosphonic dichloride (0.047 mL, 0.33 mmol). The ice bath was removed, and the reaction was stirred for 1 h. Methyl 6-aminocaproate hydrochloride (60 mg, 0.33 mmol) was added and stirring was continued for 1 h. Saturated ammonium chloride solution (10 mL) and dichloromethane (30 mL) were added. The organic layer was separated, dried over sodium sulfate, and evaporated to give **13** as a pale yellow oil. The crude phosphonic acid **13** was taken up in dichloromethane and treated with sodium carbonate (100 mg) and dimethyl sulfate (0.032 mL, 0.50 mmol). After the solution was stirred overnight at room temperature, solvent was removed under vacuum and the residue was purified by flash chromatography (CH_2Cl_2:methanol 95:5 v:v) to give **9** (46 mg, a 24% yield) as a pale yellow oil. The spectral data for this product were identical to that descibed above. **From 12, Path B.** *In situ* formation of **12** from **7** was identical to the procedure described above from **12**, path A with the exception that all amounts were doubled. The synthetic intermediate **12** was then treated with MeOH (0.066 mL, 1.5 mmol) to form **14**. The solvent was removed *in*

vacuo, acidified with 10% HCl (10 mL), extracted twice with CH_2Cl_2, dried over sodium sulfate, concentrated, and purified by flash silica chromatography (MeOH:CH_2Cl_2, 5:95; $R_f = 0.2$) to give **14** (0.061 g, 0.133 mmol) in 20% yield. Compound **14** was dissolved in CH_2Cl_2 (3 mL) followed by the addition of DCC (0.030 g, 0.146 mmol) and allowed to stir at room temperature for 15 min. A solution of 6-aminocaproic acid methyl ester hydrochloride (0.029 g, 1.59 mmol) and TEA (0.022 mL, 1.59 mmol) in CH_2Cl_2 was then added, and the mixture was allowed to stir overnight. The reaction mixture was filtered, concentrated *in vacuo*, and purified by silica chromatography (MeOH: ethyl acetate 5:95 v:v, $R_f = 0.2$) to give the methyl phosphonate **9** as a colorless oil. The spectral data for this product was identical to that described above.

8-Methyl-3*β*-(methoxyphenylphosphinyl)-8-azabicyclo-[3.2.1]octane-2*β*-carboxylic Acid *N*-(5-Carbomethoxypentyl)amide (5). To a stirred solution of **9** (0.300 g, 0.512 mmol) in MeOH (15 mL) was added 10% Pd/C (0.060 g). The flask was then charged with $H_{2(g)}$ (balloon pressure) and stirred for 2 h. The solution was filtered and the solvent removed *in vacuo* to give the *N*-desmethyl intermediate as a pale yellow oil (0.222 g, 0.491 mmol). This material was dissolved in acetonitrile followed by the addition of Na_2CO_3 (0.052 g, 0.491 mmol) and methyl iodide (0.037 mL, 0.598 mmol). The reaction mixture was allowed to stir at room temperature for 2 h and then filtered. The filtrate was concentrated *in vacuo*, and the product was purified by column chromatography (neutral aluminum oxide, MeOH:CH_2Cl_2 5:95 v:v, $R_f = 0.5$). ^{1}H NMR ($CDCl_3$): δ 1.30−1.40 m, 2H; 1.45−1.69 m, 5H; 1.78 d, 2H, $J = 16.7$; 1.88 d, J = 7.4; 1.98−2.17 m, 2H; 2.20 s, 3H; 2.23−2.32 m, 2H; 2.72 dd, 1H, J = 74.6,7.7; 3.13−3.31 m, 4H; 3.63 s, 3H; 3.69 dd 3H, J = 34.2, 11.3; 4.70 dm, J = 73.3; 7.39−7.54 m, 3H; 7.86 ddd, 2H, J = 49.5, 13.4, 8.0. ^{31}P NMR: δ 20.12, 21.01. MS (FAB): *m*/*z* 467 (M + H). Anal. Calcd for $C_{23}H_{35}N_2O_6P$: C, 59.22; H, 7.56; N, 6.00. Found: C, 59.15; H, 7.75; N, 6.20.

3*β*-(Hydroxyphenylphosphinyl)-8-methyl-8-azabicyclo-[3.2.1]octane-2*β*-carboxylic Acid *N*-(5-Carbomethoxypentyl)-amide (15). To a stirred solution of **5** (0.020 g, 0.043 mmol) under $Ar_{(g)}$ was added trimethylsilyl bromide (0.007 mL, 0.052 mmol) via syringe. The reaction was allowed to stir at room temperature for 1 h, after which trimethylsilyl bromide (0.007 mL, 0.052 mmol) was again added via syringe and the reaction was allowed to stir for an additional 1 h. Water was added (0.050 mL), and the solvent was removed *in vacuo*. The product was purified by column chromatography (C-18 solid phase extraction column, MeOH:NH_4OH (30%) 100:1 v:v) to give the product as a white solid (0.010 g, 52%). ^{1}H NMR (CD_3OD): δ 1.24−1.64 m, 7H; 1.90 s, 1H; 1.97−2.05 m, 2H; 2.20−2.28 m, 2H; 2.29−2.35 m, 2H; 2.75 s, 3H; 3.06 s, 1H; 3.10−3.19 m, 2H; 3.62 s, 3H; 3.82 s, 1H; 4.03 s, 1H; 4.65−4.80 m, 1H; 7.39−7.46 m, 3H; 7.75 dd, 2H, $J = 13.0, 7.8$. ^{31}P NMR: δ 18.53. MS (FAB): *m*/*z* 453 (M + H).

3*β*-(Hydroxyphenylphosphinyl)-8-methyl-8-azabicyclo-[3.2.1]octane-2*β*-carboxylic Acid *N*-(5-Carboxypentyl)-amide (2) Dilithium Salt. To a methanolic solution (0.665 mL) of **15** (0.040 g, 0.088 mmol) was added LiOH (1.0 N, 0.265 mL). The reaction was allowed to stir for 15 h at room temperature. The solvent was evaporated *in vacuo*, and the product was purified by column chromatography (C-18 solid phase extraction column, MeOH) to give the product as a white solid (0.023 g, 60% yield). ^{1}H NMR (CD_3OD): δ 1.24−1.34 m, 2H; 1.40−1.59 m, 4H; 1.81−1.90 m, 3H; 2.03−2.23 m, 3H; 2.09 t, 2H, J = 7.4; 2.55 s, 3H; 2.87 d, 1H, J = 5.0; 3.08−3.26 m, 2H; 3.56 s, 1H; 3.79 s, 1H; 4.57−4.62 m, 1H; 7.32−7.39 m, 3H; 7.19 dd, 2H, J = 12.6,7.7. ^{31}P NMR (CD_3OD): δ 18.86. MS (FAB): *m*/*z* 451 (M + H + 2Li), 445 (M + H + Li), 439 (M + H). Anal. Calcd for $C_{21}H_{29}Li_2N_2O_6P$: C, 56.01; H, 6.49; N, 6.22. Found: C, not available; H, 6.40; N, 6.22.

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