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Synthesis of *N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine: An Application of Lanthanide-Catalyzed Transamidation

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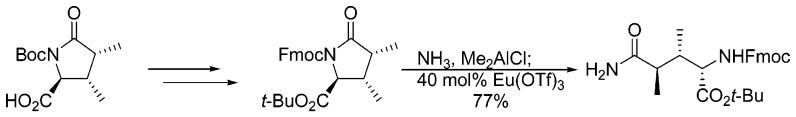

13 **7** **15**

N-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (**6**) was synthesized from *tert*-butyl *N*-Boc-(2*S*,3*S*,4*R*)-dimethylpyroglutamate (**13**). This synthesis involved selective deprotection of a Boc group from a lactam nitrogen in the presence of a *tert*-butyl ester, Fmoc protection of the lactam, and a lanthanide-catalyzed transamidation reaction of the Fmoc-protected lactam, using ammonia and dimethylaluminum chloride. The scope of Lewis acid-catalyzed transamidation of acylated lactams was explored through the variation of lanthanide, lactam, acyl group, amine, and aluminum reagent. The reactivity of various metal triflates was found to vary in the following qualitative order: Yb ~ Sc > Er ~ Eu ~ Sm > Ce ~ Ag^{I} > Cu^{II} ~ Zn. Intriguingly, catalysis was only observed when ammonia was the nitrogen nucleophile; addition of other amidoaluminum complexes to acyl lactams was found to be insensitive to the addition of lanthanides.

Introduction

The nonproteinogenic amino acid (2*S*,3*R*,4*S*)-3,4-dimethylglutamine (DiMeGln) has been found to be a key component of the cyclic depsipeptide natural products callipeltin A[1] (**1**) and papuamides A (**2**) and B (**3**).[2] Callipeltin A (**1**) was isolated from a shallow water sponge of the genus Callipelta (order Lithistida) by Minale and co-workers and shown to have both antitumor and antiHIV activities.[1] Likewise, the papuamides were isolated from the sponges Theonella mirabilis and Theonella swinhoe by Boyd and co-workers and shown to also possess both antitumor and antiHIV activities.[2] To date, syntheses of DiMeGln have been reported by Joullié,[3] Hamada,[4] and ourselves.[5] In all three cases, however, DiMeGln was synthesized with acid-labile protecting groups on N_α. In our case, an Fmoc-protected version of DiMeGln was desired for an Fmoc-based solid-phase synthesis of **1**, **2**, and related molecules. However, when the Boc-protected intermediate **4** was deprotected and reprotected with an Fmoc group under Schotten−Baumann conditions, it was found that the product **5** was a mixture of C-4 epimers, presumably as a result of acid-catalyzed enolization of the side chain amide (Scheme 1).[6] Variation of the deprotection conditions failed to alleviate this problem, so an alternate solution was sought.

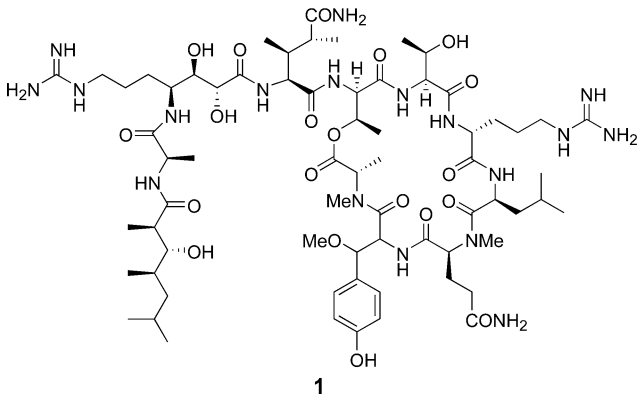

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FIGURE 1. Callipeltin A(**1**).

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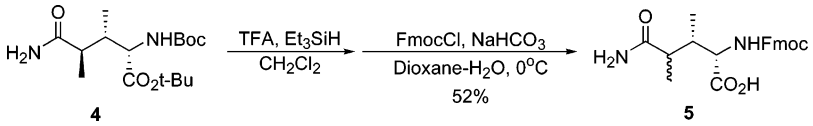

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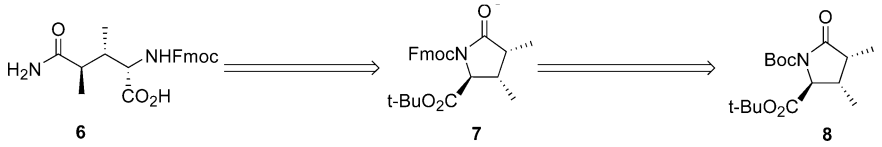

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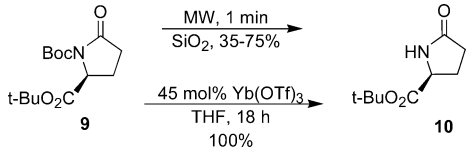

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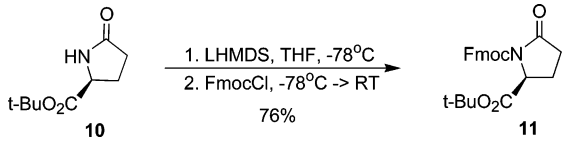

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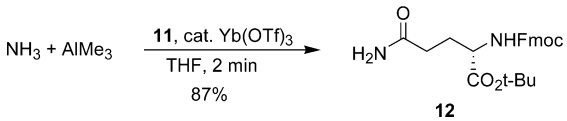

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Results and Discussion

Our revised strategy to obtain the Fmoc-protected DiMeGln residue **6** (Scheme 2) called for ammonolysis of an Fmoc-protected lactam **7** that would be synthesized from the previously synthesized intermediate **8** via selective Boc deprotection of the lactam nitrogen in the presence of the *tert*-butyl ester followed by Fmoc protection of the lactam nitrogen.

The model compound **9** (Scheme 3) was selected for its ready accessibility from commercially available (*S*)-pyroglutamic acid.[7,8] Extensive exploration revealed two methods for selective deprotection of the lactam (Scheme 3). In the first method, microwave irradiation of **9** on silica support for 1 min[9] gave the desired product **10** in 35−75% yield. Alternatively, catalytic $Yb(OTf)_3$ in THF effectively deprotected **9** after 18 h,[10] giving **10** in quantitative yield. Despite the quicker reaction time and easier workup of the microwave deprotection method, deprotection with $Yb(OTf)_3$ was adopted as the method of choice owing to variability in yields using microwave radiation.

The next step in the synthesis called for Fmoc protection of a lactam nitrogen. This was accomplished by deprotonation of the amide nitrogen of **10** with LHMDS at −78°C, followed by inverse addition of the deprotonated amide into 5 equiv of Fmoc-Cl (Scheme 4). This proceduregave the desired product, **11**, in 76% isolated yield after 14 h.

In the next step, **11** was subjected to the ammonolysis conditions that had previously worked successfully with its Boc-protected analogue **8**.[5] To our surprise, reaction of **11** with $AlMe_3-NH_3$[11] gave only 38% of the desired product **12** and after 2 h led to substantial deprotection of the Fmoc group. It was inferred from these results that the reagent was basic enough to deprotect an Fmoc carbamate. It was reasoned that, to avoid Fmoc deprotection, a faster or less basic ammonolysis reaction was needed. To this end, the use of Lewis acids as catalysts was investigated. In an early screening experiment, it was discovered that addition of catalytic $Yb(OTf)_3$ catalyzes ammonolysis of **11** by $AlMe_3-NH_3$ very efficiently (Scheme 5). After optimization studies it was determined that usage of 6−10 equiv of $AlMe_3$, addition of 40 mol % of lanthanide catalyst, and changing the solvent from CH_2Cl_2 to THF were needed to obtain high yields.

Under these conditions, ammonolysis of **11** was nearly instantaneous even at 25 °C. On the basis of these encouraging results, other Lewis acidic metal triflates—$Sc(OTf)_3$, $Er(OTf)_3$, $Eu(OTf)_3$, $Sm(OTf)_3$ $Ce(OTf)_3$, Ag-(OTf), $Cu(OTf)_2$, and $Zn(OTf)_2$—were also screened as potential catalysts of ammonolysis (Table 1). As expected,

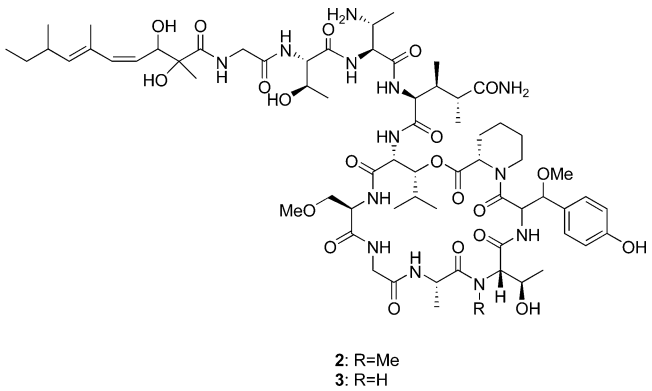

FIGURE 2. Papuamides A (**2**) and B (**3**).

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TABLE 1. Lewis Acid Catalysis of Transamidation

catalyst[a]	time, min	yield, %
–	120	38
$Yb(OTf)_3$	2	87
$Sc(OTf)_3$	2	88
$Er(OTf)_3$	5	78
$Eu(OTf)_3$	5	91
$Sm(OTf)_3$	5	91
$Ce(OTf)_3$	20	70
AgOTf	20	36
$Cu(OTf)_2$	30	24
$Zn(OTf)_2$	30	67

[a] 40 mol % used.

$Sc(OTf)_3$ was as reactive as $Yb(OTf)_3$ and both proved to be the most active Lewis acid catalysts tested. Although $Er(OTf)_3$, $Eu(OTf)_3$, and $Sm(OTf)_3$ gave slower reactions that went to completion in 5 min, reaction with $Eu(OTf)_3$ and $Sm(OTf)_3$ resulted in the production of fewer side products. The use of $Ce(OTf)_3$, AgOTf, $Cu(OTf)_2$, and $Zn(OTf)_2$ as catalysts resulted in slower reactions that were complete in 20−30 min with moderate yields (Table 1). In the best cases, the yield of ammonolysis product was improved and the time of reaction drastically reduced. It was also noted that the amount of Fmoc deprotection observed in these reactions was substantially less than that in the uncatalyzed version. Whether the decrease in Fmoc deprotection results from lessened basicity of the reagent or is simply a result of the much shorter reaction times we cannot determine.

It has also recently been shown that the use of Me_2AlCl/NH_3 affords greater reactivity than $AlMe_3/NH_3$ for the ammonolysis of sterically demanding esters.[12] All the metal triflates mentioned above were also screened with Me_2AlCl instead of $AlMe_3$. Although the reactivity trend was almost the same, and yields were slightly better (see Table 2), reactions with Me_2AlCl were slower their $AlMe_3$ counterparts.

With the methodology in hand, our efforts turned to the synthesis of the desired product **6,** beginning with the conversion of the previously synthesized intermediate **13** to its *tert*-butyl ester **8** with use of *N,N′*-diisopropyl-*O-tert*-butylisourea.[5] Selective deprotection of the lactam Boc group with catalytic $Yb(OTf)_3$ gave the lactam **14**, which was then protected with an Fmoc group in high yield. Ring opening of the Fmoc-protected lactam **7** with use of ammonia in conjunction with Me_2AlCl and $Eu(OTf)_3$ resulted in the formation of **15** in 77% isolated yield. The target compound **6** was obtained from **15** by treatment with TFA in methylene chloride in high yield. In contrast to our previous efforts, the ^1H NMR of **6** showed no evidence of epimerization. With the synthesis of **6** thus completed, it was decided to further investigate the scope of lanthanide-catalyzed transamidation by examining the reaction of *N*-Fmoc-caprolactam (**16**) in addition to **7** and **11** (Table 2).

Except in the case of **7**, lanthanide-catalyzed ammonolysis of Fmoc-protected lactams (**7**, **11**, and **16**) gave higher yields and shorter reaction times compared to the uncatalyzed reactions. In addition to the Fmoc-protected lactams, Boc-protected lactam **9** was also subjected to ammonolysis reaction conditions. Interestingly, even with the NH_3 no significant catalytic activity with the addition of metal triflates was observed. Amines other than NH_3 were also tried with **11**, but in no case was catalysis by the added lanthanide triflate observed.

TABLE 2. Lanthanide-Catalyzed Transamidation of Lactams

amine	lactam	Al reagent	catalyst[a]	time, min	yield, %
NH_3	**7**	$AlMe_3$	–	120	61
NH_3	**7**	$AlMe_3$	$Yb(OTf)_3$	10	32
NH_3	**7**	Me_2AlCl	–	120	25
NH_3	**7**	Me_2AlCl	$Eu(OTf)_3$	30	77
NH_3	**11**	$AlMe_3$	–	120	38
NH_3	**11**	$AlMe_3$	$Yb(OTf)_3$	2	87
NH_3	**11**	Me_2AlCl	$Eu(OTf)_3$	10	91
NH_3	**16**	$AlMe_3$	–	60	40
NH_3	**16**	Me_2AlCl	$Eu(OTf)_3$	60	90
NH_3	**9**	$AlMe_3$	–	10	85
NH_3	**9**	$AlMe_3$	$Yb(OTf)_3$	10	86
$PhCH_2NH_2$	**11**	$AlMe_3$	–	5	80
$PhCH_2NH_2$	**11**	$AlMe_3$	$Yb(OTf)_3$	10	80
$PhCH_2NH_2$	**11**	Me_2AlCl	$Eu(OTf)_3$	40	87
Et_2NH	**11**	$AlMe_3$	–	180	*b*
Et_2NH	**11**	$AlMe_3$	$Yb(OTf)_3$	60	*b*
t-$BuNH_2$	**11**	$AlMe_3$	–	360	*c*
t-$BuNH_2$	**11**	$AlMe_3$	$Yb(OTf)_3$	360	*c*

[a] 40 mol %. [b] Fmoc deprotection. [c] Partial Fmoc deprotection.

Conclusion

In summary, *N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (**6**) was synthesized in 57% overall yield in five steps starting from *tert*-butyl *N*-Boc-(2*S*,3*S*,4*R*)-3,4-dimethylpyroglutamate (**13**). It was also shown that lanthanide triflates catalyze the ammonolysis of Fmoc-protected lactams in conjunction with $AlMe_3$ or Me_2AlCl. These conditions offer a way to ammonolyze even sterically hindered, Fmoc-protected lactams. With compound **6** in hand, total syntheses of the callipeltins and papuamides are actively under way.

Experimental Section

General Procedure for Boc Deprotection of Lactams with Catalytic $Yb(OTf)_3$. To a solution of Boc-protected lactam in THF (2 mL) was added $Yb(OTf)_3$ (45 mol %). The mixture was stirred at room temperature for 18 h and the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (2 mL) and solution filtered through a fine pore sintered glass funnel. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

***tert*-Butyl (2*S*,3*S*,4*R*)-3,4-Dimethylpyroglutamate (14).** The general procedure for Boc deprotection of lactam was followed with use of *tert*-butyl *N*-Boc-(2*S*,3*S*,4*R*)-3,4-dimethylpyroglutamate (**8**) (89 mg, 0.285 mmol) and $Yb(OTf)_3$ (79 mg, 0.114 mmol). Flash column chromatography with 50% EtOAc/petroleum ether yielded **14** as a colorless, flocculent crystalline solid (57 mg, 95%): mp 61 °C; IR (NaCl, cm^{-1}) 3233 (br), 2975, 2934, 2871, 1735, 1709, 1458, 1393, 1219, 1158; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (br s, 1H), 3.67 (d, 1H, 4.7 Hz), 2.64−2.53 (m, 2H), 1.49 (s, 9H), 1.16 (d, 3H, 6.74 Hz), 1.11 (d, 3H, 7.18 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 170.9, 82.4, 61.4, 39.1, 37.8, 28, 14.6, 10.4 ppm; HRMS (CI) calcd for $C_{11}H_{19}NO_3$ (M+) 214.1443, found 214.1446.

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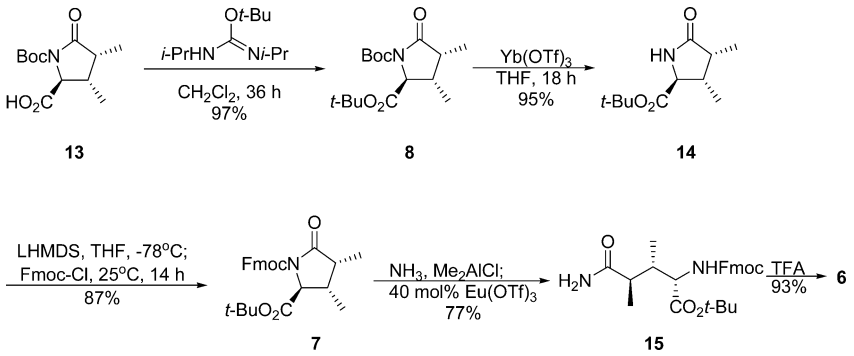
SCHEME 6



General Procedure for the Fmoc Protection of Lactams. To a solution of the lactam in THF at −78 °C was added LHMDS (0.95 equiv, 1 M solution in THF) slowly. The resultant pale yellow mixture was stirred at −78 °C for 15 min, and slowly transferred by cannula to a solution of Fmoc-Cl (5 equiv) in THF at −78 °C. The reaction was allowed to stir at −78 °C for 2 h, after which it was allowed to rise to room temperature. After 14 h of stirring at room temperature, the reaction was quenched by addition of sat. NH_4Cl (2 mL) and H_2O (1 mL). The solution was extracted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

***tert*-Butyl *N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylpyroglutamate (7).** The general procedure for Fmoc protection of lactam was followed with use of *tert*-butyl (2*S*,3*S*,4*R*)-3,4-dimethylpyroglutamate **(14)** (27 mg, 0.13 mmol) in THF (2 mL). Flash column chromatography with 20% EtOAc/petroleum ether yielded **7** as a colorless oil (48 mg, 87%): IR (NaCl, cm^{-1}) 3066, 2977, 2935, 2978, 1798, 1761, 1722, 1478, 1451, 1387, 1369, 1303, 1156; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 4H, 7.6 Hz), 7.41−7.24 (m, 4H), 4.55−4.3 (m, 3H), 4.14 (s, 1H), 2.85 (p, 1H, 7 Hz), 2.50 (p, 1H, 7 Hz), 1.44 (s, 9H), 1.16 (d, 3H, 7 Hz), 1.10 (d, 3H, 7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 169.6, 151.9, 143.6 143.4, 141.3, 141.2, 127.8, 127.3, 125.5, 119.9, 82.6, 69, 64.9, 46.7, 40.7, 34.7, 27.9, 15.4, 9.9 ppm; HRMS (ESI) calcd for $C_{26}H_{29}NO_5$ (Na+) 458.1943, found 458.1945.

***tert*-Butyl N^{α}-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (15).** To a solution of Me_2AlCl (2.52 mL of a 1 M solution in CH_2Cl_2, 2.52 mmol) in CH_2Cl_2 (4 mL) at −8 °C was bubbled gaseous NH_3 for 4 min. The reaction was allowed to stir at −8°C for 15 min and allowed to warm to room temperature. Over 30 min CH_2Cl_2 was removed by using a flow of nitrogen gas to afford a colorless slurry. The residue was added to THF (7 mL) and allowed to stir at 25 °C for a minute. Lactam **7** (110 mg, 0.252 mmol) and $Eu(OTf)_3$ (60 mg, 0.10 mmol) in THF (1.1 mL) was added to the reaction mixture. After 30 min the reaction was quenched with 0.1 N HCl (25.2 mL, 2.52 mmol) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc. Organic fractions were combined, washed with brine, and dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by flash column chromatography with 50% EtOAc/hexane followed by 80% EtOAc/hexane, yielding **15** as a colorless oil (88 mg, 77%): IR (NaCl, cm^{-1}) 3345 (br), 3203, 3066, 2975, 2936, 1716, 1662, 1516, 1452, 1427, 1369, 1345, 1156; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.60 (d, 2H, 7 Hz), 7.45−7.27 (m, 4H), 6.83 (br, 1H), 5.64 (d, 1H, 8.8 Hz), 5.57 (br, 1H), 4.60−4.55 (m, 1H), 4.46−4.40 (m, 1H), 4.25−4.17 (m, 1H), 2.37 (dd, 1H, 6.5, 3.5 Hz), 1.82 (br, 1H), 1.49 (s, 9H), 1.16 (d, 3H, 7 Hz), 0.94 (d, 3H, 7 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 170.7, 156.8, 143.7, 143.4, 141.4, 141.3, 127.8, 127.1, 125.0, 124.9, 120.0, 119.9, 82.9, 66.9, 57.6, 47.3, 41.6, 40.0, 27.9, 16.1, 12.4 ppm; HRMS (ESI) calcd for $C_{26}H_{32}N_2O_5$ (Na+) 475.2209, found 475.2213.

***N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (6).** A solution of *tert*-butyl *N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (**15**) (88 mg, 0.20 mmol) in 30% TFA−CH_2Cl_2 (1.5 mL) was allowed to stir at room temperature for 90 min. Removal of solvent and TFA by evaporation under reduced pressure yielded *N*-Fmoc-(2*S*,3*S*,4*R*)-3,4-dimethylglutamine (**6**) as a fine, colorless powder (72 mg, 93%): mp >210 °C dec; IR (NaCl, cm^{-1}) 3323 (br), 3066, 2923, 2851, 1702, 1671, 1609, 1515, 1450, 1412, 1319, 1227, 1034; ^1H NMR (300 MHz, C_2D_6SO) δ 7.89 (d, 2H, 7.6 Hz), 7.75 (d, 2H, 6.5), 7.44−7.33 (4H, m), 6.82 (s, 1H), 4.25 (br s, 3H), 4.15 (m, 1H), 2.34 (t, 1H, 7 Hz), 1.97 (br s, 1H), 1.42 (s, 1H), 1.09 (d, 3H, 6.4 Hz), 0.87 (d, 3H, 5.9 Hz) ppm; ^{13}C NMR (75 MHz, C_2D_6SO) δ 181, 174.5, 158.7, 145.5, 145.3, 142.7, 128.3, 126.5, 126.3, 121.2, 121.1, 68.2, 57.4, 48.3, 44.0, 40.5, 16.9, 10.5 ppm; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_5$ (Na+) 419.1583, found 419.1583.

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Supporting Information Available: Complete experimental descriptions of transformations not included in the Experimental Section and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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