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Reactions of In Situ Generated *N*-Boc Nitrones with Aromatic and Heteroaromatic Grignard Reagents: Application to the Synthesis of Zileuton

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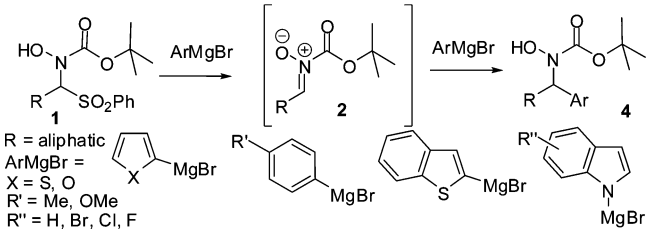
Received December 3, 2007



A new class of α-aromatic-*N*-hydroxylamines has been prepared by reaction of *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates with aromatic and heteroaromatic Grignard reagents. Reactions proceed via a base-assisted elimination of the phenylsulfonyl group leading to *N*-Boc nitrones. This methodology has been applied to the synthesis of zileuton.

Creation of the carbon−carbon bond remains a major challenge for organic chemists. The use of organometallic reagents is particularly attractive due to their huge nucleophilicity and structural diversity. Among them, Grignard reagents are powerful tools for the synthetic chemist since they are in most cases readily available, well-known, and very reactive toward numerous electrophilic entities.[1] In particular, the addition of such reagents to the carbon−nitrogen double bond of imines and their derivatives (hydrazones, oximes) is a powerful method to prepare a wide range of amino compounds which are used in organic synthesis as important intermediates.[2] However, the basicity of Grignard reagents is often a problem encountered when performing nucleophilic additions to imines, promoting competitive enolization. This side reaction can be overcome by the use of more electrophilic imines, bearing an electron-withdrawing group on the nitrogen atom.[3] However, because of their intrisic high reactivity, these electrophilic imines are more sensitive to moisture, they are unstable,[3g] and/or the deprotection of the reaction products sometimes requires harsh conditions. Nitrones,[4] which can be considered as imine *N*-oxides, present advantages of being both more electrophilic and more stable than their imines derivatives. That is why numerous additions of organometallic reagents have been performed on nitrones over the last years, leading to *N*-hydroxylamine derivatives, which are valuable building blocks in organic synthesis.[4b,c,5] We recently developed an original method to prepare *N*-(*tert*-butoxycarbonyl) (*N*-Boc)-protected propargylic, allylic, and homoallylic *N*-hydroxylamines via in situ generation of *N*-Boc-protected nitrones by reaction between *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1** and organometallic reagents (Figure 1).[6] The undeniable advantage of using the *N*-(*tert*-butoxycarbonyl) group resides in the fact that it can be easily cleaved under mild conditions allowing synthesis of hydrogenolysis-sensitive compounds and/or primary *N*-hydroxy amino moiety.

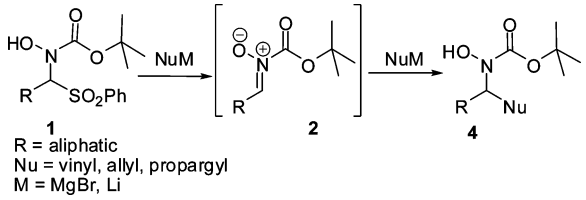


FIGURE 1. Reaction of in situ generated *N*-Boc nitrones **2** with unsaturated organometallics.

Herein, we wish to report the reactions of these *N*-Boc nitrones precursors with aromatic and heteroaromatic Grignard reagents, leading to α-aromatic and α-heteroaromatic-*N*-Boc-*N*-hydroxylamines **4**, **6**, **7**, and **11** in good to excellent yields and an application in the synthesis of zileuton.

Compounds **1a**−**e** were easily prepared from aldehydes, *tert*-butyl *N*-hydroxycarbamate, and sodium benzenesulfinate in MeOH/H_2O or H_2O/THF in the presence of formic acid according to our previous report.[6] We first studied the reaction of monocyclic heteroaromatic and aromatic Grignard reagents, such as 2-thienyl- and 2-furylmagnesium bromides **3a**[7] and **3b**,[8] respectively, and arylmagnesium bromides **5a**,**b** with various *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1** (Table 1). Best conditions were found when sulfone **1a** was reacted with **3a** in toluene during 45 min at room temperature leading to compound **4a** in 88% yield, versus 51% in THF. The application of these conditions to sulfones **1b**−**d** gave corresponding α-thienyl-*N*-(Boc)-*N*-hydroxylamines **4b**−**d** in 74%, 47%, and 54% yields, respectively. When the reaction was

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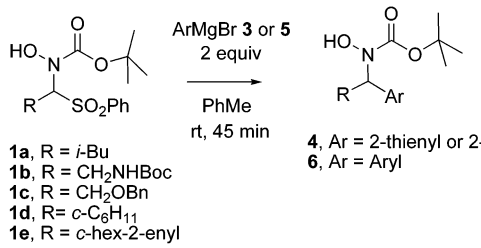
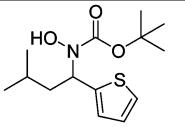
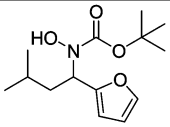
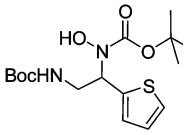
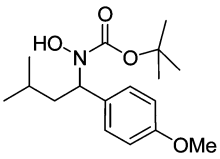
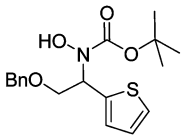
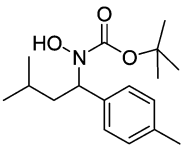
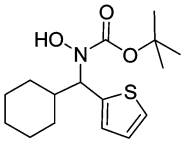
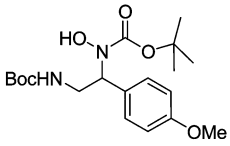
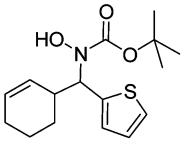
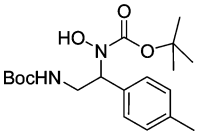
10.1021/jo7025838 CCC: $40.75
Published on Web 02/13/2008

TABLE 1. Reactions of Sulfones 1 with Heteroaromatic and Aromatic Grignard Reagents



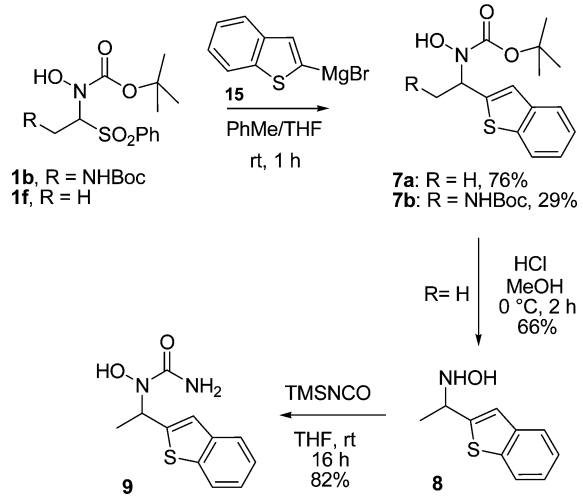
N-hydroxylamine	yield	*N*-hydroxylamine	yield
	**4a**, 88%[a]		**4f**, 86%[d]
	**4b**, 74%[b]		**6a**, 97%[d]
	**4c**, 47%		**6b**, 83%[d]
	**4d**, 54%		**6c**, 55%[b,d]
	**4e**, 64%[c]		**6d**, 63%[b,d]

[a] 51% yield when the reaction was performed in THF. [b] 3 equiv of Grignard reagent. [c] dr: 0.7/1. [d] Reaction performed in THF/PhMe (1/5) solution.

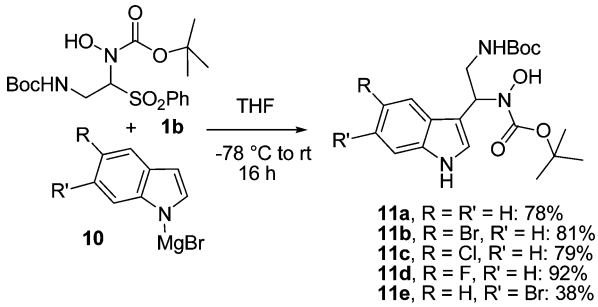
performed on *β*-chiral sulfone **1e**, *N*-hydroxylamine **4e** was obtained with a poor level of diastereoselectivity. These conditions were then applied to the reaction of sulfone **1a** with 2-furylmagnesium bromide **3b**, prepared by metalation of furan with *n*-butyllithium in the presence of TMEDA followed by transmetalation with magnesium bromide diethyl etherate.[8] α-Furyl-*N*-(Boc)-*N*-hydroxylamine **4f** was obtained in excellent yield. Finally, the reaction of tolylmagnesium bromide **5a** and 4-methoxyphenylmagnesium bromide **5b** with sulfones **1a** and **1b** afforded the corresponding α-phenyl-*N*-(Boc)-*N*-hydroxylamines **6a**−**d** in good yields (Table 1).

We then focused on the reaction of *N*-Boc nitrones with bicyclic heteroaromatic Grignard reagents such as 2-benzothienylmagnesium bromide **15** (Scheme 1) and various indolylmagnesium bromides **10** (Scheme 2). Indeed, the benzothiophene and the indole moieties are widely represented in bioactive products.[9] Compound **15** was prepared by metalation of benzothiophene with *n*-butyllithium followed by transmetalation with magnesium bromide diethyl etherate.[10] Reactions of

SCHEME 1. Reaction of Sulfones 1b and 1f with 2-Benzothienylmagnesium Bromide: Synthesis of Zileuton 9



SCHEME 2. Reaction of Sulfone 1b with Indolylmagnesium Bromides 10



2-benzothienyl Grignard **15** with sulfones **1b** and **1f**[6] afforded the corresponding α-benzothien-2-yl-*N*-Boc-*N*-hydroxylamines **7a** and **7b** in 76% and (unoptimized) 29% yields, respectively (Scheme 1).

N-Boc *N*-hydroxylamine **7a** was then engaged in the synthesis of zileuton **9** (Ziflo),[11] a compound belonging to the *N*-hydroxyurea class.[12] Zileuton is the first selective, orally active inhibitor of the 5-lipoxygenase, an enzyme implicated in the biosynthesis of leukotrienes which are implicated as mediators in disease states[13] such as asthma, allergy, psoriasis, and inflammatory bowel disease. Several syntheses of zileuton have been described within either racemic[14] or enantioselective pathways.[10,15]

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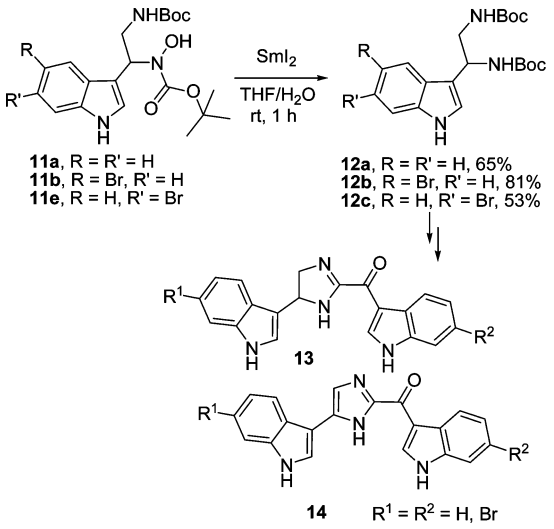
SCHEME 3. Synthesis of Di-*N*-Boc Indolic 1,2-Diaminoethanes 12a-c



N-Hydroxylamine **7a** was deprotected with hydrochloric acid in Merino's conditions,[16] and the reaction of the resulting primary *N*-hydroxylamine **8** with trimethylsilyl isocyanate afforded racemic zileuton **9** in the excellent overall yield of 31% in four steps from the commercially available *tert*-butyl *N*-hydroxycarbamate.

Finally, we studied the reactions of sulfone **1b** with indolylmagnesium bromides **10**, obtained by metalation of the corresponding indolic cores with methylmagnesium bromide.[17] We prepared α-indol-3′-yl-*N*-Boc-*N*-hydroxylamines **11a**−**e** in excellent yields (Scheme 2). It is noteworthy that no transmetalation occurred when halogenated indoles were used, allowing access to halogenated products. The reduction of the *N*-OH bond in compounds **11a**, **11b**, and **11e** with samarium(II) diiodide afforded 1,2-diamino indolic compounds **12a**−**c** which could be key intermediates in the synthesis of marine sponge alkaloids[18,19] of the spongotine and topsentin classes **13** and **14** (Scheme 3).

In conclusion, we have developed a novel method for the synthesis of α-aryl-*N*-hydroxyamino compounds via the reaction of *N*-Boc nitrone precursors **1a**−**e** with aromatic and heteroaromatic Grignard reagents. We have shown that this reaction is very general concerning the choice of the organometallic reagent. We have applied this new methodology to the synthesis of zileuton in an overall yield of 31% in four steps from the commercially available *tert*-butyl *N*-hydroxycarbamate. Finally, we have prepared the di-*N*-Boc indolic 1,2-diaminoethanes **12a**−**c**, potential building blocks in the total syntheses of spongotine and topsentin marine sponge products **13** and **14**.

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Experimental Section

1-[*N*-(*tert*-Butoxycarbonyl)-*N*-hydroxyamino]-3-methyl-1-(thien-2-yl)butane (4a). To a stirred solution of sulfone **1a** (200 mg, 0.58 mmol) in toluene (4 mL) under inert atmosphere was added 2 equiv of 2-thienylmagnesium bromide (1.16 mL, 1.16 mmol, 1 M solution in toluene) at room temperature. The resulting mixture was stirred during 45 min before being quenched by addition of an aqueous saturated solution of ammonium chloride. The mixture was then extracted three times with EtOAc. The organic layers were washed with brine and dried over anhydrous magnesium sulfate. After the removal of the solvent, the crude mixture was then purified by column chromatography on silica gel (eluent: CH_2Cl_2) to give the pure product **4a** (145 mg, 0.51 mmol). Yield: 88%. IR (film): 3211, 2961, 2931, 2871, 1686, 1476, 1399, 1319, 1236, 1170, 1136, 1096, 1043 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (d, J = 5.9 Hz, 3H, CH_3), 0.96 (d, J = 5.9 Hz, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.55−1.75 (m, 2H, CH_2), 2.05−2.20 (m, 1H, CH), 5.33 (dd, J = 5.6 and 9.8 Hz, 1H, CHN), 6.93 (dd, J = 3.7 and 4.9 Hz, 1H, H arom), 7.00 (d, J = 3.2 Hz, 1H, H arom), 7.10 (s, 1H, OH), 7.18 (d, J = 4.9 Hz, 1H, H arom). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.7 (CH_3), 22.9 (CH_3), 24.8 (CH), 28.3 ($C(CH_3)_3$), 41.7 (CH_2), 56.1 (CHN), 82.1 ($C(CH_3)_3$), 124.5 (CH arom), 125.2 (CH arom), 126.3 (CH arom), 142.6 (C arom), 156.7 (C═O). LRMS (ESI): m/z = 292 [(M + Li)$^+$], 577 [(dimer + Li)$^+$]. Anal. Calcd for $C_{14}H_{23}NO_3S$: C, 58.92; H, 8.13; N, 4.91. Found: C, 59.27; H, 8.22; N, 4.83.

1-[*N*-(*tert*-Butoxycarbonyl)-*N*-hydroxyamino]-1-(benzothien-2-yl)ethane (7a). To a solution of thianaphthene (89 mg, 0.66 mmol) in ether (1 mL) at room temperature was added *n*-BuLi (1.28 M in hexane 0.52 mL, 0.66 mmol). After 55 min of reaction, $MgBr_2{\cdot}OEt_2$ (171 mg, 0.66 mmol) was added in three portions to give a suspension of 2-benzothienylmagnesium bromide. To this solution was added a solution of sulfone **1f** (100 mg, 0.33 mmol) in toluene (4 mL) and THF (1 mL). The resulting mixture was allowed to stir at room temperature during 1 h. It was then quenched by addition of a saturated aqueous solution of ammonium chloride. Aqueous layers were extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on flash silica gel (eluent: CH_2Cl_2). The product **7a** was obtained as a pale amorphous solid (73 mg, 0.25 mmol). Yield: 76%. IR (KBr): 3213, 3150, 2962, 2869, 1681, 1408, 1389, 1325, 1157, 1101, 1011 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 9H, $C(CH_3)_3$), 1.71 (d, J = 6.9 Hz, 3H, CH_3), 5.48 (dq, J = 1.0 and 7.0 Hz, 1H, CHN), 7.20 (s, 1H, H arom), 7.18−7.35 (m, 2H, H arom), 7.65−7.80 (m, 2H, H arom). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.0 (CH_3), 28.2 ($C(CH_3)_3$), 54.5 (CHN), 82.6 ($C(CH_3)_3$), 121.5, (CH arom), 122.2 (CH arom), 123.4 (CH arom), 124.2 (CH arom),139.4 (C arom), 139.5 (C arom),144.5 (C arom), 156.6 (C═O). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.78. Found: C, 61.19; H, 6.70; N, 4.70.

1-(*N*-Hydroxyamino)-1-(benzothien-2-yl)ethane (8). A cold solution of hydrochloric acid was prepared at 0 °C by adding 271 μL (300 mg, 3.82 mmol) of freshly distilled acetyl chloride to 1 mL of dry methanol. The resulting solution was stirred for 15 min at 0 °C. A solution of *N*-hydroxylamine **7a** (80 mg, 0.273 mmol) in 0.7 mL of methanol was then added to the acidic solution at 0 °C, and the resulting mixture was stirred for an additional 2 h. Methanol was then slowly evaporated under vacuum (temperature <20 °C). The residue was dissolved in EtOAc, and to the resulting mixture was added a saturated solution of sodium hydrogenocarbonate. It was then extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2). The product **8** was obtained as a yellow amourphous solid (34 mg, 0.18 mmol). Yield: 66%. IR (KBr): 3171, 3049, 2977,

2865, 1453, 1366, 1310, 1082 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.51 (d, $J = 6.6$ Hz, 3H, CH_3), 4.45 (q, $J = 6.6$ Hz, 1H, CHN), 7.19 (s, 1H, H arom), 7.24−7.39 (m, 2H, H arom), 7.69−7.74 (m, 1H, H arom), 7.74−7.81 (m, 1H, H arom). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 19.7 (CH_3), 57.9 (CHN), 121.3 (CH arom), 122.3 (CH arom), 123.3 (CH arom), 124.1 (CH arom), 124.2 (CH arom), 139.3 (C arom), 139.5 (C arom), 146.6 (C arom). LRMS (ESI): *m*/*z* 194 [$(M + H)^+$], 217 [$(M + Na)^+$]. Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 61.88; H, 5.77; N, 7.05.

Zileuton (9). To a solution of primary hydroxylamine **8** (30 mg, 0.155 mmol) in THF (10 mL) was added TMSNCO (89 mg, 0.77 mmol) at room temperature, and the resulting solution was stirred for 16 h. Several drops of water were then introduced, and the resulting mixture was stirred for an additional 30 min. The mixture was concentrated in vacuo, and the residue was triturated with CH_2Cl_2, collected, washed with CH_2Cl_2, and dried to give zileuton (**9**) as a white solid (30 mg, 0.127 mmol). Yield: 82%. IR (film): 3468, 3318, 3270, 3191, 2876, 1651, 1573, 1456, 1434, 1157 cm^{-1}. ^1H NMR (DMSO, 300 MHz): δ 1.51 (d, $J = 6.9$ Hz, 1H, CH_3), 5.57 (q, $J = 6.9$ Hz, 1H, CHN), 6.41 (s, 2H, NH_2), 7.26 (s, 1H, H arom), 7.25−7.37 (m, 2H, H arom), 7.73−7.79 (m, 1H, H arom), 7.85−7.90 (m, 1H, H arom), 9.22 (s, 1H, H arom). ^{13}C NMR (DMSO, 75.5 MHz): δ 17.8 (CH_3), 52.3 (CHN), 121.2 (CH arom), 122.1 (CH arom), 123.2 (CH arom), 123.9 (CH arom), 124.0 (CH arom), 138.9 (C arom), 139.0 (C arom), 146.1 (C arom), 163.3 (C═O). LRMS (ESI): *m*/*z* 237 [$(M + H)^+$], 259 [$(M + Na)^+$], 275 [$(M + K)^+$].

1-[*N*-(*tert*-Butoxycarbonyl)-*N*-hydroxyamino]-2-[*N*-(*tert*-butoxycarbonyl)amino]-1-(indol-3′-yl)ethane (11a). To a solution of indole (127 mg, 1.08 mmol) in THF (3 mL) at −78 °C under inert atmosphere was added methylmagnesium bromide (0.36 mL, 1.08 mmol, 3 M solution in Et_2O), and the resulting solution was stirred during 15 min. A solution of the sulfone **1b** dissolved into THF was slowly added, and the reaction was allowed to reach −5 °C over a few hours and was stirred overnight. It was then quenched by addition of an aqueous saturated solution of ammonium chloride. The crude mixture was extracted three times by EtOAc. The organic layers were washed by an aqueous saturated solution of sodium chloride and then dried over anhydrous magnesium sulfate. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel (eluent: CH_2Cl_2 then EtOAc) to yield **11a** as a colorless solid (103 mg, 0.28 mmol). Yield: 78%. IR (film): 3332, 3057, 2980, 2932, 2872, 1695, 1515, 1457, 1395, 1366, 1288, 1251, 1169, 1111 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 9H, $C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 3.20−3.28 (m, 1H, CH of CH_2N), 3.85−4.05 (m, 1H, CH of CH_2N), 5.06 (br s, 1H, NHBoc), 5.44 (dd, $J = 4.2$ and 11.4 Hz, 1H, CHN), 7.04 (dt, $J = 1.0$ and 7.2 Hz, 1H, H indol), 7.10 (t, $J = 6.9$ Hz, 1H, H indol), 7.18 (s, 1H, H indol), 7.26 (d, $J = 7.8$, 1H, H indol), 7.63 (d, $J = 7.5$ Hz, 1H, CH indol), 8.28 (s, 1H, NH indol). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.4 (2 $C(CH_3)_3$), 41.4 (CH_2N), 55.1 (CHN), 80.6 ($C(CH_3)_3$), 81.1 ($C(CH_3)_3$), 111.2 (CH indol), 112.2 (C indol), 119.1 (CH indol), 119.7 (CH indol), 122.1 (CH indol), 123.1 (CH indol), 126.4 (C indol), 135.7 (C indol), 156.4 (C═O), 158.0 (C═O). LRMS (ESI): *m*/*z* 398 [$(M + Li)^+$], 414 [$(M + Na)^+$], 789 [$(dimer + Li)^+$], 805 [$(dimer + Na)^+$]. HRMS (ESI): calcd for $C_{20}H_{29}N_3O_5Na$ [$(M + Na)^+$] 414.2005, found 414.2007.

Acknowledgment. We thank ACI no. 02L0525, "Nouvelles approches thérapeutiques du cancer", for financial support. This research work was supported by a grant from the Ministère de la Jeunesse, de l'Education Nationale et de la Recherche to X.G.

Supporting Information Available: Experimental procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7025838