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USEFUL SYNTHESIS OF THE LONGER ARRAY OXAZOLE RINGS FOR TELOMESTATIN

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Abstract - The convenient syntheses of the precursors of the constituting Fragments A, B, A-B, and its macrocyclic compounds for telomestatin, which exhibits strong antitumor activity, were first achieved.

A metabolite telomestatin (**1**),^{1,2} isolated from the culture of *Streptomyces anulatus* 3533-SV4, has a very unique macrocyclic structure constituting of oxazole and thiazoline rings only, as shown in Figure 1. Not only the interesting structure but also the bioactivity of **1**, exhibiting strong antitumor activity, attracted us to investigate its total synthesis and structure-bioactivity relationships. So far, it has been already known that various oxazole-4-carboxylates are derived from hydroxylated α -amino acid,³⁻⁵ its dipeptide,^{5,6} α -dehydroamino acid,^{5,7} its dehydropeptide⁷ and so on. However, the synthesis of 2-(1-amino-2-hydroxyalkyl)polyoxazole-4-carboxylates by the oxazolation of dehydropeptide has not been reported yet. Here, for the total synthesis of **1**, the promising precursors of the protected Fragment A and B, benzyl 2-(2-{2-[1-(*N*-Boc)amino-2-(*O*-TPS)hydroxyethyl]-5-methyloxazol-4-yl}-5-methyl-oxazol-4-yl)oxazole-4-carboxylate (**17**) [(**P**)-**2**] and methyl 2-(2-{2-[1-(*N,O*-Isop-*N*-Cbz)amino-2-hydroxyethyl]oxazol-4-yl}oxazol-4-yl)oxazole-4-carboxylate (**24**) [(**P**)-**3**] were first synthesized.

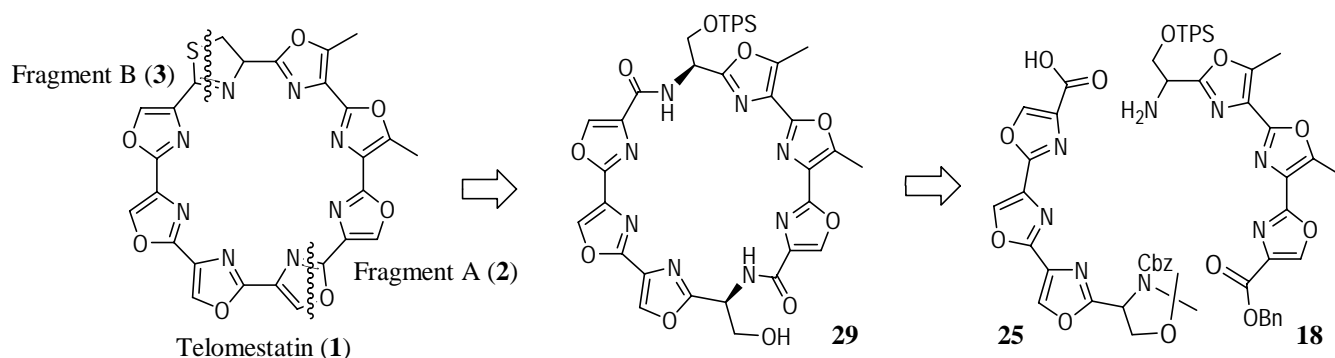
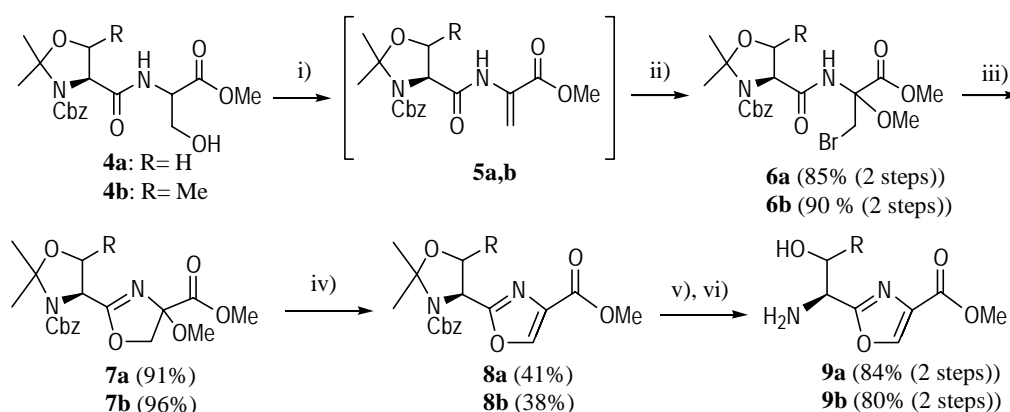


Figure 1. Retrosynthesis of **1**.

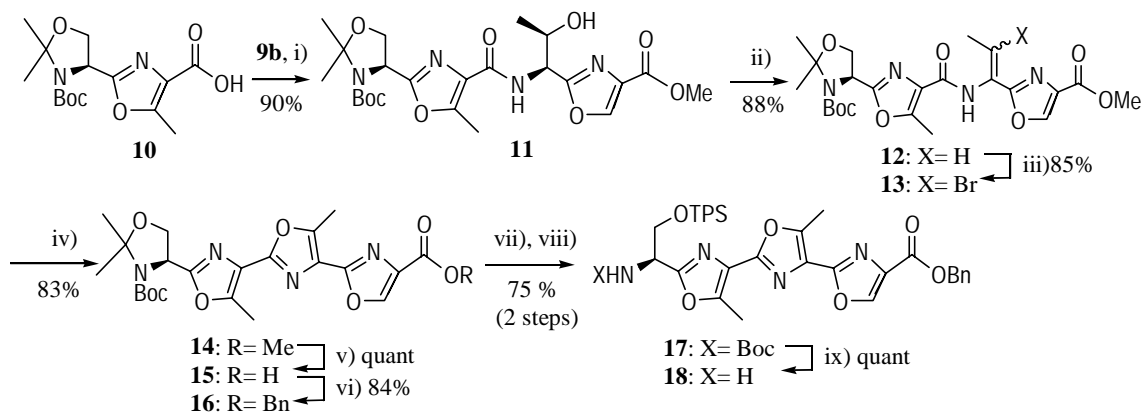
Furthermore, fragment condensation between Fragments A and B for Fragment A-B and its macrocyclization are also described. (Boc=*t*-butoxycarbonyl, TPS=*t*-butyldiphenylsilyl, Isop= isopropylidene, Cbz=benzyloxycarbonyl).

First, to synthesize methyl 2-(1-amino-2-hydroxyalkyl)oxazole-4-carboxylate (**9**: **a**; R=H, **b**; R=Me) as the important constructing block, β -elimination of OH group of the C-terminal Ser residue of *N,O*-Isop-*N*-Cbz-L-Ser-L-Ser-OMe (**4a**)- or -L-Thr-L-Ser-OMe (**4b**) with methanesulfonyl chloride (MsCl) in the presence of Et₃N and DBU⁸ gave the corresponding Δ^2 -dehydride⁹ derivative (**5a,b**). Without purification, bromination with NBS (*N*-bromosuccinimide) in MeOH^{5,10,11} gave the expected α -methoxy- β -bromoalaninedipeptide (**6a,b**). According to the method reported,¹² subsequent cyclization of **6a,b** with Cs₂CO₃ gave 4-methoxyoxazoline derivative (**7a,b**), the MeO group of which was β -eliminated with CSA to give the corresponding oxazole derivative (**8a,b**).¹³ Deprotection of the Isop group of **8a,b** with TFA and CHCl₃ (4 : 96 v/v), followed by deprotection of Cbz group with 10% Pd-C/H₂ gave the expected **9a,b**¹⁴ (Scheme 1).



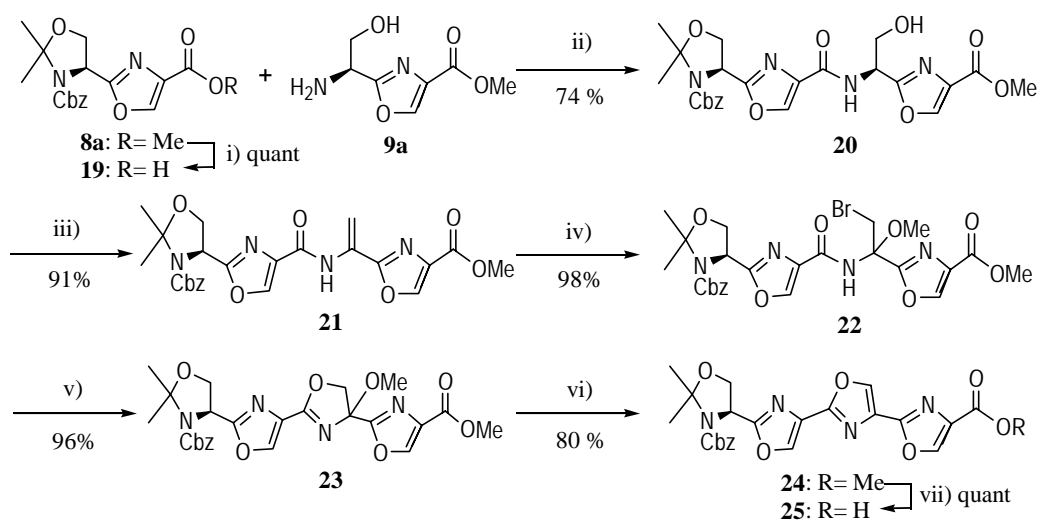
Scheme 1. Reagents and conditions: i) a) MsCl, Et₃N/ CHCl₃, b) DBU/ CHCl₃, ii) NBS, MeOH/ THF, iii) Cs₂CO₃/ Dioxane, 60°C, iv) cat. CSA/ Toluene, 70°C, v) 4% TFA-CHCl₃, vi) H₂, 10% Pd-C/ MeOH

Secondly, to synthesize the precursor of **2**, after preparing *N*-Boc-*N,O*-Isop-5-methyloxazole-4-carboxylic acid (**10**), derived by bromination and then oxazolation of *N*-Boc- Δ^2 -dehydride,¹⁴ coupling of **10** with **9b** using BOP¹⁵ as a condensing agent and (*i*-Pr)₂NEt gave the corresponding 2-(5-methyloxazoloyl)oxazolidipeptide (**11**). Similarly to the case of **5**, consecutive β -elimination of the OH group of **11** with MsCl and then DBU, followed by bromination of the formed dehydride (**12**) with NBS in CHCl₃ in place of MeOH gave β -bromodehydride derivative (**13**), which was oxazolated with Cs₂CO₃¹⁵ to give the protected trisoxazole derivative (**14**). After ester hydrolysis with 1 M LiOH, the obtained free acid (**15**) was again esterified with BnBr. The Isop group of the obtained Bn ester (**16**) was deprotected with 4% TFA and then protected with TPSCl to give the corresponding 2-[1-(*N*-Boc)amino-2-(*O*-TPS)hydroxyethyl]trisoxazole derivative **17** [(**P**)-**2**],¹⁶ the Boc group of which was finally deprotected with TFA to give the precursor of **2** (**18**), almost quantitatively (Scheme 2).



Scheme 2. Reagents and conditions: i) BOP, (*i*-Pr)₂NEt/ DMF, ii) a) MsCl, Et₃N/ CHCl₃, b) DBU/ CHCl₃, iii) a) NBS/ CHCl₃, b) Et₃N/ CHCl₃, iv) Cs₂CO₃/ Dioxane, 60°C, v) 1M LiOH/ MeOH, vi) BnBr, Et₃N/ DMF, vii) 4% TFA-CHCl₃, viii) TPSCl, Imidazole/ DMF, ix) TFA-CHCl₃(2:3)

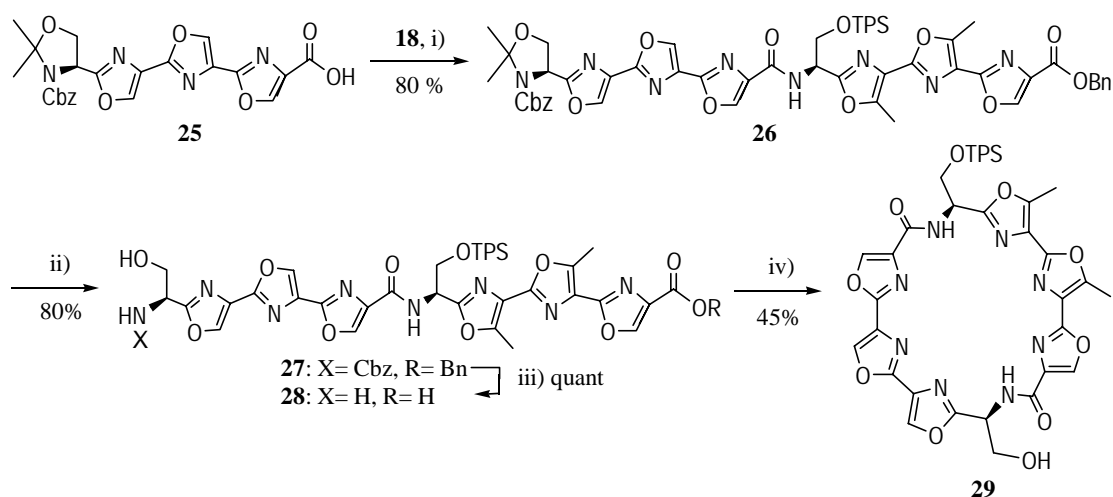
Thirdly, to synthesize the precursor of **3**, hydrolysis of methyl ester part of **8a** with 1 M LiOH, followed by condensation of the formed free acid (**19**) with **9a** using BOP gave the 2-oxazoloyloxazolidipeptide (**20**). Furthermore, similarly to the above cases as shown in Schemes 1 and 2, the successive β -elimination of OH group of **20** to the dehydridipeptide (**21**), α -methoxy- β -bromination of **21** to the β -bromo- α -methoxy derivative (**22**), oxazolation of **22** to the methoxyoxazoline (**23**) and β -elimination of MeO group of **23** afforded the desired trisoxazole methyl ester (**24**)[(P)-**3**].¹⁷ Subsequently, the ester part of **24** was hydrolyzed with 1 M LiOH to give the precursor of **3** (**25**), almost quantitatively (Scheme 3).



Scheme 3. Reagents and conditions: i) 1M LiOH/ MeOH, ii) BOP, (*i*-Pr)₂NEt/ DMF, iii) a) MsCl, Et₃N/ CHCl₃, b) DBU/ CHCl₃, iv) NBS/ MeOH, v) Cs₂CO₃/ Dioxane, 60°C, vi) cat. CSA/ Toluene, 70°C, vii) 1M LiOH/ MeOH

Finally, fragment condensation of **25** with **18** by the BOP method gave the protected

2-[2-[1-(*N*-aminoethyl)trioxazoloyl]trioxazole]-4-carboxylate derivative (**26**), the Isop group of which was *in situ* deprotected with 4% TFA-CHCl₃ to give the corresponding benzyl 2-[1-(*N*-Cbz)hydroxyethyl]polyoxazole-4-carboxylate derivative (**27**).¹⁸ Lastly, after deprotection of Cbz and Bn groups of **27** with 10% Pd-C/H₂ in MeOH, macrocyclization of the formed both *N*- and *C*-termini free compound (**28**) using BOP and *N*-hydroxybenztriazole (HOBT) in the presence of (*i*-Pr)₂NEt and DMAP in DMF under high dilution conditions (1 mmol/L) proceeded smoothly to give the expected macrocyclic compound (**29**)¹⁹ [colorless amorphous material, 45% yield. MALDI-TOF MS Found: *m/z* 951.27 (M + Ag)⁺. Calcd for C₄₂H₃₈N₈O₁₀Si: 950.82 (M + Ag)⁺] (Scheme 4).



Scheme 4. Reagents and conditions: i) BOP, (*i*-Pr)₂NEt/ DMF ii) 4% TFA-CHCl₃ iii) H₂, 10% Pd-C/ MeOH, iv) BOP, HOBT, (*i*-Pr)₂NEt, DMAP/ DMF (1 mmol/ l).

In conclusion, it is noteworthy that convenient synthesis of the two kinds of trioxazole sequences, their coupling and then macrocyclization were first achieved in short steps by novel method. Further investigations on the total synthesis of **1** are currently under way in our laboratory.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. K. Shin-ya, K. Wierzba, K. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa, and H. Seto, *J. Am. Chem. Soc.*, 2001, **123**, 1262.
2. M. Y. Kim, H. Vankayalapati, K. Shin-ya, K. Wierzba, and L. H. Hurley, *J. Am. Chem. Soc.*, 2002, **124**, 2098.

3. D. A. Evans, J. R. Gege, and J. L. Leightow, *J. Am. Chem. Soc.*, 1992, **114**, 9434.
4. K. S. Cardwell, S. A. Hermitage, and A. Sjolín, *Tetrahedron Lett.*, 2000, **41**, 4239.
5. S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon, and D. Waite, *J. Chem. Soc., Perkin Trans. I*, **2000**, 2415.
6. P. Wipf and C. P. Miller, *Tetrahedron Lett.*, 1992, **33**, 907.
7. a) C. Shin, Y. Nakamura, and K. Okumura, *Chem. Lett.*, **1993**, 1405, b) K. Okumura, A. Ito, H. Saito, Y. Nakamura, and C. Shin, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2309.
8. C. Shin, A. Okabe, A. Ito, A. Ito, and Y. Yonezawa, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1583.
9. In this paper, the symbol Δ^2 indicates the position number of double bond of α -dehydroamino acid residue from the *N*-terminus in sequence.
10. C. Shin, K. Nanjo, and J. Yoshimura, *Tetrahedron Lett.*, **1974**, 521.
11. C. Shin, Y. Sato, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1909.
12. J. Das, J. A. Reid, D. R. Kronenthal, J. Singh, P. D. Pansegrau, and R. H. Mueller, *Tetrahedron Lett.*, 1992, **33**, 7835.
13. **8a**: Colorless powder. mp 55.5-56.0 °C (from hexane and EtOAc). $[\alpha]_D^{26} -10.6^\circ$ (*c* 1.00, CHCl₃). IR(KBr): 3412, 3101, 2947, 2369, 1711, 1589 cm⁻¹. ¹H NMR (DMSO-*d*₆) δ =1.52 and 1.62 (each s, 6H, C(CH₃)₂), 3.80 (s, 3H, COOCH₃), 4.08 (dd, 1H, *J*=2.0, 9.2Hz, β -H), 4.27 (dd, 1H, *J*=6.3, 9.2 Hz, β -H), 4.92 and 5.82 (each d, 2H, *J*=12.9 Hz, Cbz-CH₂), 5.25(dd, 1H, *J*=2.0, 6.3 Hz, α -H), 7.09-7.38 (m, 5H, Cbz's Ph), 8.77 (s, 1H, ring-H).
8b: Colorless powder. mp 92.5-93.5 °C (from hexane and EtOAc). $[\alpha]_D^{26} -68.9^\circ$ (*c* 1.03, CHCl₃). IR (KBr): 3412, 3133, 2991, 1707, 1591cm⁻¹. ¹H NMR (DMSO-*d*₆) δ =1.24 (d, 3 x 1/3 H, *J*=5.4 Hz, γ -H), 1.26 (d, 3 x 2/3 H, *J*=6.1 Hz, γ -H), 1.54, 1.59 and 1.62 (each s, 6H, C(CH₃)₂), 3.78 (s, 3 x 1/3 H, COOCH₃), 3.80 (s, 3 x 2/3 H, COOCH₃), 4.23-4.26 (m, 1H, β -H), 4.65-5.08 (m, 3H, α -H and Cbz-CH₂), 6.97-7.35 (m, 5H, Cbz' Ph), 8.67 (s, 1 x 2/3 H, ring-H), 8.85 (s, 1 x 1/3 H, ring-H).
14. H. Saito, T. Yamada, K. Okumura, Y. Yonezawa, and C. Shin, *Chem. Lett.*, **2002**, 1098.
15. BOP: Benzyltriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.
16. **17**: Colorless syrup. $[\alpha]_D^{26} -3.3^\circ$ (*c* 0.18, CHCl₃). IR (KBr): 3447, 3365, 2959, 2932, 1725, 1713, 1692 cm⁻¹. ¹H NMR (CDCl₃): δ 0.99 (s, 9H, TPS's *t*-Bu), 1.46 (s, 9H, Boc's *t*-Bu), 2.69 and 2.82 (each s, 6H, ring-CH₃ x 2), 3.98-4.17 (m, 2H, β -H), 5.06 (m, 1H, α -H), 5.39 (s, 2H, Bn's CH₂), 5.53 (br d, 1H, BocNH, *J*=9.1 Hz), 7.29-7.56 (m, 15 H, TPS's Ph x 2 and Bn's Ph), 8.29 (s, 1H, ring-H).
Anal. Calcd for C₄₂H₄₆N₄O₈Si: C, 66.12; H, 6.08; N, 7.34. Found: C, 65.88; H, 5.98; N, 7.73.
17. **24**: Colorless powder. mp 208-209 °C (from hexane and EtOAc). $[\alpha]_D^{26} -8.6^\circ$ (*c* 0.95, CHCl₃). IR (KBr): 2361, 2340, 1719, 1410 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.54 and 1.68 (each s, 6H, C(CH₃)₂), 3.84 (s, 3H, COOCH₃), 4.14(dd, 1H, *J*=2.0, 9.5 Hz, β -H), 4.30(dd, 1H, *J*=6.3, 9.5 Hz, β -H),

- 4.93 and 5.11 (each s, 2H, Cbz's CH₂, $J=12.6$ Hz), 5.32 (dd, 1H, $J=2.0, 6.3$ Hz, α -H), 7.10-7.34 (m, 5H, Cbz's Ph), 8.92, 9.00 and 9.09 (each s, 3H, ring-H x 3). *Anal.* Calcd for C₂₄H₂₂N₄O₈: C, 58.30; H, 4.48; N, 11.33. Found: C, 58.21; H, 4.46; N, 11.50
18. **26**: Colorless syrup. $[\alpha]_D^{26} -41.1^\circ$ (c 0.18, CHCl₃). IR (KBr): 3410, 3159, 2955, 2932, 1721, 1710, 1689, 1630, 1589 cm⁻¹. ¹H NMR (CDCl₃): δ 1.02 (s, 9H, TPS's *t*-Bu), 2.70 and 2.80 (each s, 6H, ring-CH₃ x 2), 3.25(br s, 1H, OH), 4.04-4.12 (m, 2H, TPSO-CH₂), 4.17-4.24 (m, 2H, HO-CH₂), 5.06-5.12 (m, 3H, HO-CH₂CH and Cbz's CH₂), 5.54 (s, 2H, Bn's CH₂), 5.54-5.61 (m, 1H, TPSO-CH₂CH), 6.15 (br s, 1H, CbzNH,), 7.28-7.65 (m, 20H, TPS's Ph x 2, Cbz's Ph and Bn's Ph), 7.77 (br d, 1H, CONH, $J=8.9$ Hz), 8.26, 8.28, 8.28, and 8.29 (each s, 4H, ring-H x 4). *Anal.* Calcd for C₅₇H₅₂N₈O₁₃Si: C, 63.09; H, 4.83; N, 10.33. Found: C, 63.12; H, 4.92; N, 10.17.
19. **29**: Colorless amorphous material. Diastereomer (1:1). $[\alpha]_D^{23} -4.5^\circ$ (c 0.1, CHCl₃). IR(KBr): 3437, 2928, 2855, 1676, 1670, 1663, 1597, 1508 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 0.85 and 0.89 (eachs, 9H, TPS's *t*-Bu), 2.69, 2.70, 2.77 and 2.78 (each s, 6H, ring-CH₃ x 2), 3.84-4.26 (m, 4H, HOCH₂ and TPSOCH₂), 5.18-5.40 (m, 2H, NHCH), 7.26-7.56 (m, 10H, TPS's Ph), 8.22-8.41 (m, 2H, CONH x 2), 8.85, 8.89, 8.91, 8.93, 8.95, 9.09, 9.12, 9.13 (each s, 4H, ring-H x 4). *Anal.* Calcd for C₄₂H₃₈N₈O₁₀Si: C, 59.85; H, 4.56; N, 13.29. Found: C, 60.12; H, 4.52; N, 13.17. MALDI-TOF MS Found: m/z 951.27 (M + Ag)⁺. Calcd for C₄₂H₃₈N₈O₁₀Si: 950.82 (M + Ag)⁺.