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Attempted Synthesis of Spongidines by a Radical Cascade Terminating onto a Pyridine Ring

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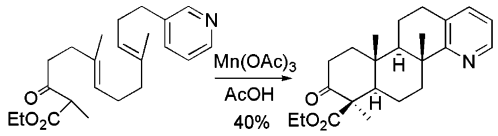

Mn(III)-based oxidative free-radical cyclization of an unsaturated β-keto ester containing a pyridine ring as radical trap has been studied. This intramolecular reaction of nucleophilic carbon-centered radicals with the pyridine ring leads to the stereospecific construction of a tetracyclic compound in which five chiral centers are created in one pot. This synthetic approach represents the first attempt to prepare the anti-inflammatory pyridinium alkaloids spongidine A, B, and D.

The selective functionalization of aromatic heterocycles is of great importance to the pharmaceutical industry in its quest for new drugs. The Minisci radical alkylation offers a unique method of functionalizing electron-deficient aromatic heterocycles.[1] Nucleophilic addition of an alkyl radical to a protonated heterocycle followed by re-aromatization can allow carbon alkylation. We were interested in this type of reaction and, in particular, an intramolecular version since intramolecular reactions of nucleophilic carbon-centered radicals with aromatic systems are often of synthetic value for the construction of polycyclic compounds incorporating aromatic rings.[2] Despite its apparent utility, few synthetically useful examples have been reported with heteroaromatic substrates such as pyridines. For example, a few intramolecular cyclizations with tin-based reagents have been reported.[3−5] Several tin-free radical cyclizations onto a pyridine ring have also been described using Mn(III) acetate,[6] xanthate-mediated chemistry,[7] and to the best of our knowledge, the only known example of an intramolecular Minisci-type reaction.[8]

Biomimetic polyolefin carbocyclizations are one of the most powerful one-step constructions known in biochemistry or synthetic chemistry.[9] Since Breslow and co-workers achieved in 1968 the cyclization of farnesyl acetate with benzoyloxy radicals,[10] cyclizations based on radical transformations have been exploited successfully in several polycyclizations leading to the formation of terpene and steroid frameworks.[11] In 1990, Snider developed manganese(III)-based oxidative free-radical cyclizations,[12] and this work led to the formation of a wide variety of fused ring systems.[13] Normally, these radical cyclizations are initiated with β-keto esters and terminate by addition to olefins or benzene rings, though cyclizations terminated by addition to furans[14] and azides[15] have been described recently.

With this background in mind, we envisaged a novel manganese(III)-based polyolefin triple radical cyclization terminating onto a pyridine ring, which would lead to the tetracyclic carbon framework **5** (Scheme 1) present in spongidine A (**1**), B (**2**), and D (**4**)(Figure 1), new pyridinium alkaloids isolated from marine sponges which have shown antiinflammatory activity.[16]

Herein, we disclose the first synthetic approach of spongidines using a stereospecific construction of a tetracyclic compound in which five chiral centers are created in one pot. This tetracyclic compound leads to the formation of isomeric compounds of natural spongidines.

According to our strategy, outlined in Scheme 1, the key reaction is the cyclization mediated by $Mn(OAc)_3$ of acyclic precursor **6** to give the tetracyclic compound **5** which possess the carbon skeleton present in natural spongidines A, B, and D. As can be seen in Scheme 1, the success of our key reaction will depend on the regiochemistry of the final attack of the tertiary alkyl radical onto the pyridine ring, which could be attacked either at position 2 (ortho attack) or position 4 (para attack) as desired. It is known that 3-substituted pyridines are alkylated intermolecularly by tertiary alkyl radicals (*tert*-butyl radical) exclusively at position 6 due to steric effects.[17] However, Citterio and co-workers have reported that intramolecular alkylation of 3-substituted pyridines by tertiary alkyl radicals takes place leading to ca. 1:1 mixtures of cyclization products at positions 2 and 4.[6] Therefore, the regiochemistry of our key reaction was a priori unknown. Precursor **6** could be synthesized

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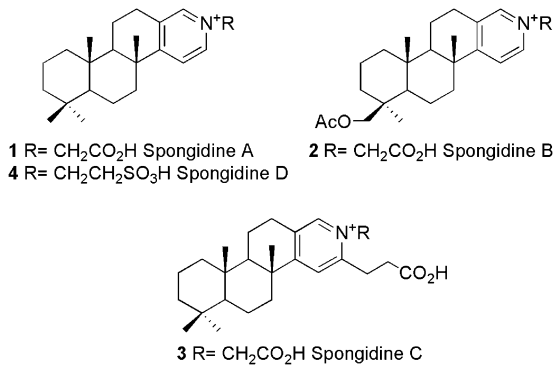
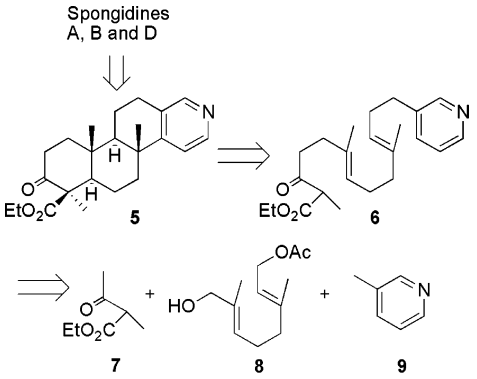
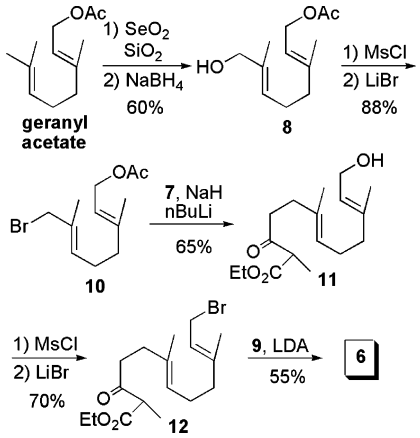


FIGURE 1. Chemical structures of natural spongidines.

SCHEME 1. Retrosynthetic Analysis of Spongidines A, B, and D



SCHEME 2. Synthesis of Acyclic Precursor 6



from commercially available methyl acetoacetate **7** and picoline **9** and readily synthesized geranyl acetate **8**.

The synthesis of polyene **6** began with the allylic oxidation with SeO_2 in the presence of silica of commercially available geranyl acetate,[18] which gave alcohol **8** in 60% overall yield (Scheme 2). Allylic alcohol **8** was converted using MsCl and LiBr into bromide **10** in 88% yield, which upon treatment with methyl acetoacetate **7** dianion furnished the allylic alcohol **11** in 65% yield. Alcohol **11** was converted using MsCl and LiBr into *E*,*E*-bromide **12** in 70% yield, which was coupled with the lithium anion of picoline **9** to give the acyclic precursor **6** in 55% yield.

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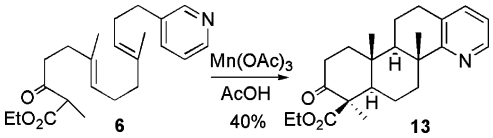
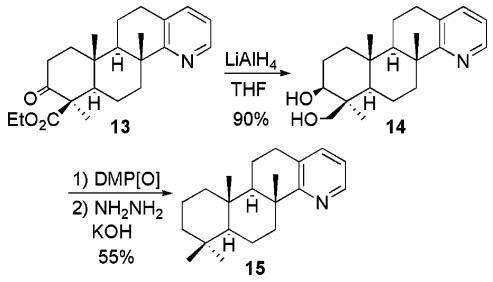
SCHEME 3. Radical Polycyclization of Precursor 6



SCHEME 4. Functionalization in Ring A of Tetracycle 13



Radical-mediated cyclization of compound **6** using the Snider method[19] gave the tetracyclic β-keto ester **13** in 40% yield with no other identifiable compound isolated from the reaction mixture (Scheme 3). The ^{1}H and ^{13}C NMR signals of **13** were assigned by different 2D NMR and NOE difference experiments and comparison with reported data.[20,21] In particular, the aromatic part of the ^{1}H NMR spectrum of **13** was especially indicative of the pattern of coupling of the assigned chemical structure, since there were two doublets of coupling constants at 7.5 and 4.5 Hz, respectively, and a double doublet with the above-mentioned coupling constants. Diagnostic NOESY cross-peaks were detected between the angular methyl groups and the ester group confirming the assigned stereostructure. Unfortunately, the desired cyclized product, compound **5**, was not detected. Thus, the final cyclization went to the ortho position, position 2, of the pyridine ring instead of the desired attack of the final tertiary radical to the para position, position 4, of the pyridine ring. Despite obtaining undesired products, this reaction is the result of a highly stereoselective radical cyclization terminating onto the piridine ring present in precursor **6**. Thus, with this method we are able to produce isomeric structures of natural spongidines, whose biological properties can be studied.

Therefore, with the tetracycle **13** in hand, we continued the elaboration of the functionalization present in ring A of spongidines (Scheme 4). Thus, the conversion of the β-keto ester moiety into the *gem*-dimethyl group was carried out in three reaction steps: reduction to the corresponding diol **14**, oxidation to a β-keto aldehyde, and a double Wolf−Kischner reduction to give isomeric spongidine **15**. Further derivatization of compound **15** for biological evaluation is under investigation.

In conclusion, we have evaluated the scope of one radical-based cascade reaction involving a pyridine ring as radical trap toward spongidines (Scheme 1). Our attempts to carry out the radical-mediated reaction with the substrate **6**, leading to **5**, instead led to the isomeric spongidine structure **13** (Scheme 3). Therefore, these studies have demonstrated how interesting and unpredictable some radical reactions can be. This is particularly so when several alternative reaction pathways are presented to

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radical intermediates by neighboring functionality in a constrained environment, as found in the substrate **6**. These same radical reactions frequently offer the opportunity to elaborate novel and unusual structures and ring systems not available by more conventional synthetic methods, e.g., the polycycle **13**.

Experimental Section

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dienyl Acetate (8). A suspension of selenium oxide (2,8 g, 25 mmol) and *tert*-butyl hydroperoxide (70%, 14 mL, 100 mmol) in anhydrous dichloromethane (150 mL) was stirred for 20 min at room temperature, and then silica gel (230−400 mesh, 25 g) was added. After 30 min, the geranyl acetate (11 mL, 50 mmol) was slowly added. The mixture was stirred for 24 h, filtered through Celite, and washed with 10% potassium hydroxide and brine. The extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting dark orange residue was dissolved in 13 mL of ethanol and cooled to 0 °C, and sodium borohydride (1,5 g, 40 mmol) was added in several portions. After 30 min, a saturated solution of NH_4Cl (5 mL), brine, and ethyl acetate was added. The mixture was extracted with ethyl acetate and once with dichloromethane, dried, and concentrated. The residue was purified by flash chromatography eluting with hexane/AcOEt (8/2, v/v) to give known[16] alcohol **8** as a yellow oil (6,3 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30−5.40 (2H, m), 4.58 (2H, d, J = 7), 3.95 (2H, s), 2.05−2.25 (4H, m), 2.06 (3H, s), 1.71 (3H, s), 1.66 (3H, s).

(2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dienyl Acetate (10). A solution of alcohol **8** (8.35 g, 39 mmol) in dichloromethane (160 mL) at −40 °C was treated with triethylamine (11 mL, 78 mmol) followed by mesyl chloride (6.2 mL, 78 mmol) dropwise. After 90 min, T = −20 °C, a solution of lithium bromide (8.5 g, 97 mmol) in THF (40 mL) was added and stirring continued overnight. After 15 h, the mixture was quenched with saturated solution of NH_4Cl, extracted with DCM, dried, and concentrated under vacuum. The resulting residue was chromatographed eluting with hexane/AcOEt (9/1, v/v) to give bromide **10** as a yellow oil (9.4 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45−5.60 (1H, m), 5.33 (1H, m), 4.57 (2H, d, J = 7), 3.97 (2H, d, J = 14), 2.05 (3H, s), 1.74 (3H, s), 1.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (s), 141.4 (s), 132.4 (s), 130.4 (d), 118.8 (d), 61.2 (t), 52.3 (t), 41.5 (t), 38.5 (t), 26.3 (t), 21.0 (q), 16.4 (q), 14.6 (q); HRMS (EI) calcd for $C_{12}H_{19}O_2$-Br 274.0568 [M^+], found 274.0564.

(6*E*,10*E*)-Ethyl 12-Hydroxy-2,6,10-trimethyl-3-oxododeca-6,-10-dienoate (11). To a suspension of sodium hydride (2.9 g, 72 mmol) in THF (170 mL) and HMPA (3 mL) at 0 °C was added ethyl methyl acetoacetate (11.2 mL, 72 mmol) dropwise over 30 min. After 10 min, *n*-BuLi (2.5 M, 29 mL, 72 mmol) was added dropwise to the above mixture over 30 min. After 1 h under stirring at 0 °C, a solution of the allylic bromide **10** (4 g, 14.5 mmol) in THF (15 mL) was added via syringe over 20 min and stirring continued overnight. After 15 h, the reaction mixture was quenched with saturated solution of of NH_4Cl, the layers were separated, and the aqueous phase was extracted with DCM, dried, and concentrated under vacuum. The resulting residue was chromatographed on silica eluting with hexane/AcOEt (from 8/2 to 6/4, v/v) to give β-keto ester **11** (2.8 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (1H, t, J = 7), 5.07 (1H, t, J = 7), 4.16 (2H, q, J = 7), 4.12 (2H, d, J = 7), 3.49 (1H, q, J = 7), 2.23 (2H, t, J = 7), 1.64 (3H, s), 1.57 (3H, s), 1.30 (3H, d, J = 7), 1.25 (3H, t, J = 7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (s), 170.5 (s), 139.0 (s), 133.5 (s), 124.5 (d), 123.6 (d), 61.3 (t), 59.2 (t), 52.8 (d), 39.9 (t), 39.2 (t), 33.1 (t), 26.0 (t), 16.1 (q), 16.0 (q), 14.0 (q), 12.7 (q); HRMS (EI) calcd for $C_{17}H_{28}O_4$ 296.1988 [M^+], found 296.1992.

(6*E*,10*E*)-Ethyl 12-Bromo-2,6,10-trimethyl-3-oxododeca-6,10-dienoate (12). A solution of alcohol **11** (2.8 g, 9.4 mmol) in dichloromethane (35 mL) at −40 °C was treated with triethylamine (2 mL, 14.4 mmol) followed by mesyl chloride (1.1 mL, 14.4 mmol) dropwise. After 90 min, a solution of lithium bromide (1.3 g, 14.4 mmol) in THF (14 mL) was added and stirring continued during an additional 2 h. Then, the mixture was quenched with a saturated solution of NH_4Cl and extracted with DCM, dried, and concentrated under vacuum. The resulting residue was chromatographed eluting with hexane/AcOEt (8/2, v/v) to give bromide **12** as an orange oil (2.3 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (1H, dt, J = 8, 1), 5.08 (1H, t, J = 5.6), 4.17 (2H, q, J = 7), 4.08 (2H, d, J = 8), 3.50 (1H, q, J = 7), 2.25 (2H, t, J = 8), 1.71 (3H, s), 1.58 (3H, s), 1.32 (3H, d, J = 7), 1.26 (3H, t, J = 7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (s), 170.5 (s), 142.4 (s), 134.0 (s), 124.2 (d), 120.4 (d), 61.3 (t), 52.8 (d), 41.1 (t), 40.0 (t), 39.2 (t), 33.1 (t), 26.0 (t), 16.1 (q), 16.0 (q), 14.1 (q), 12.7 (q); HRMS (EI) calcd for $C_{17}H_{27}O_3Br$ 358.1144 [M^+], found 358.1140.

(6*E*,10*E*)-Ethyl 2,6,10-Trimethyl-3-oxo-13-(pyridin-3-yl)trideca-6,10-dienoate (6). A solution of diisopropylamine (1.4 mL, 10 mmol) in THF (8 mL) at 0 °C was treated with *n*-BuLi (2.5 M, 4 mL, 10 mmol) dropwise and stirred for 15 min. Then, HMPA (1 mL) was added followed by the picoline **9** (0.98 mL, 10 mmol) dropwise. The resulting red solution was stirred for 15 min, and the bromide **12** (0.9 g, 2.5 mmol) in THF (3 mL) was added. The reaction mixture was stirred overnight. After 15 h, the mixture was quenched by addition of a saturated solution of NH_4Cl, diluted with ethyl acetate, washed with brine, dried, and concentrated under vacuum. The resulting residue was chromatographed eluting with hexane/AcOEt (from 6/4 to 5/5, v/v) to afford polyene precursor **6** as a yellowish oil (0.51 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40−8.43 (2H, m), 7.48 (1H, d, J = 8), 7.18 (1H, dd, J = 7.5, 4.7), 5.10 (2H, m), 4.17 (2H, q, J = 7), 3.51 (1H, q, J = 7), 1.57 (3H, s), 1.50 (3H, s), 1.31 (3H, d, J = 7), 1.25 (3H, t, J = 7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (s), 170.5 (s), 149.9 (d), 147.1 (d), 137.4 (s), 136.3 (s), 135.9 (d), 133.4 (s), 124.9 (d), 123.1 (d), 122.8 (d), 61.3 (t), 52.8 (d), 40.1 (t), 39.4 (t), 33.2 (t), 33.1 (t), 29.4 (t), 26.5 (t), 16.0 (q), 15.9 (q), 14.0 (q), 12.7 (q); HRMS (EI) calcd for $C_{23}H_{33}O_3N$ 371.2460 [M^+], found 371.2457.

Radical Cyclization of Precursor 6 To Afford Tetracycle (±)-13. To a suspension of $Mn(OAc)_3$ (0.7 g, 2.6 mmol) in degassed acetic acid (6 mL) was added a solution of the precursor **6** (0.33 g, 0.89 mmol) in degassed acetic acid (3 mL) over 15 min under a helium atmosphere at room temperature. After being stirred for 15 h, the mixture was poured carefully into a saturated solution of $NaHCO_3$ and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The resulting orange residue was chromatographed on silica eluting with hexane/AcOEt (6/4, v/v) to furnish the tetracyclic compound **13** as a yellowish semisolid (0.13 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (1H, d, J = 4.6), 7.32 (1H, d, J = 7.5), 7.00 (1H, dd, J = 7.5, 4.6), 4.17 (2H, m), 3.02 (1H, ddd, J = 14.8, 14.7, 6.6), 2.89 (1H, dd, J = 17.2, 6.2), 2.78 (1H, m), 2.71 (1H, ddd, J = 13.6, 2.9, 2.9), 2.42 (1H, ddd, J = 14.8, 4.7, 2.2), 2.20 (2H, m), 1.94 (1H, m), 1.75 (1H, dq, J = 12.1, 6.4), 1.38 (3H, s), 1.28 (3H, t, J = 4), 1.27 (3H, s), 1.10 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7 (s), 173.6 (s), 166.1 (s), 146.8 (d), 136.7 (d), 129.6 (s), 120.7 (d), 61.1 (t), 57.6 (d), 57.5 (s), 53.9 (d), 40.5 (s), 40.4 (t), 38.6 (t), 37.7 (s), 36.5 (t), 29.2 (t), 23.7 (q), 20.8 (q), 20.6 (t), 18.1 (t), 13.9 (q), 13.8 (q); HRMS (EI) calcd for $C_{23}H_{31}O_3N$ 369.2304 [M^+], found 369.2283.

Reduction of Tetracycle 13 to Diol (±)-14. To a solution of the keto ester **13** (70 mg, 0.19 mmol) in THF (5 mL) was added lithium aluminum hydride (43 mg, 1.1 mmol) in one portion, and the mixture was refluxed for 20 h. Then, water and 15% NaOH were added, and the mixture was diluted with ethyl acetate and extracted. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude diol **14** (58 mg, 90%) was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (1H, d, J = 4.5), 7.31 (1H, d, J = 7.5), 6.98 (1H, dd, J = 7.5, 4.5), 4.23 (1H, d, J = 11.1), 3.42 (1H, d, J = 11.1), 1.24 (3H, s), 1.18 (3H, s), 0.91 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (s), 146.5 (d), 136.7 (d), 129.8

(s), 120.6 (d), 80.4 (d), 64.2 (t), 55.7 (d), 55.0 (d), 42.6 (s), 40.6 (s), 39.2 (t), 37.9 (t), 37.0 (s), 29.3 (t), 27.6 (t), 24.0 (q), 22.6 (q), 18.6 (t), 17.7 (t), 16.9 (q); HRMS (EI) calcd for $C_{21}H_{31}O_2N$ 329.2355 [M^+], found 329.2350.

Conversion of Diol 14 into Tetracycle (±)-15. Dess−Martin periodinane (174 mg, 0.41 mmol) was added to a solution of the diol **14** (58 mg, 0.17 mmol) in DCM (1 mL) at room temperature, under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h, diethyl ether (10 mL) was added, and then the resulting suspension was poured into a saturated solution of sodium thiosulfate and sodium bicarbonate (1:1, 10 mL) and stirred vigorously for 30 min. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and then evaporated in vacuo to leave a yellowish oil, which was used in the next step without further purification.

A solution of the ketone−aldehyde (44 mg, 0.13 mmol), potassium hydroxide (85%, 450 mg, 6.9 mmol), and hydrazine (110 μL, 2.3 mmol) in diethylene glycol (1 mL) was stirred at 120 °C for 2 h. Then, the temperature was brought to 220 °C and maintained for 1 h. The reaction mixture was cooled, poured into saturated solution of NH_4Cl, and extracted with ethyl acetate. The resulting residue was chromatographed on silica eluting with hexane/AcOEt (1/1, v/v) to afford pyridine **15** as a yellowish oil (26 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (1H, d, J = 4.5), 7.32 (1H, d, J = 7.8), 6.98 (1H, dd, J = 7.5, 4.8), 1.25 (6H, s), 1.22 (3H, s), 0.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5 (d), 136.7 (d), 130.1 (s), 120.5 (d), 54.2 (d), 53.1 (d), 40.6 (s), 39.2 (t), 38.1 (t), 37.3 (s), 36.5 (t), 30.6 (q), 29.7 (t), 29.7 (s), 29.3 (t), 24.1 (q), 21.4 (t), 21.2 (t), 20.4 (q), 17.7 (t), 14.1 (q); HRMS (EI) calcd for $C_{21}H_{31}N$ 297.2457 [M^+], found 297.2450.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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