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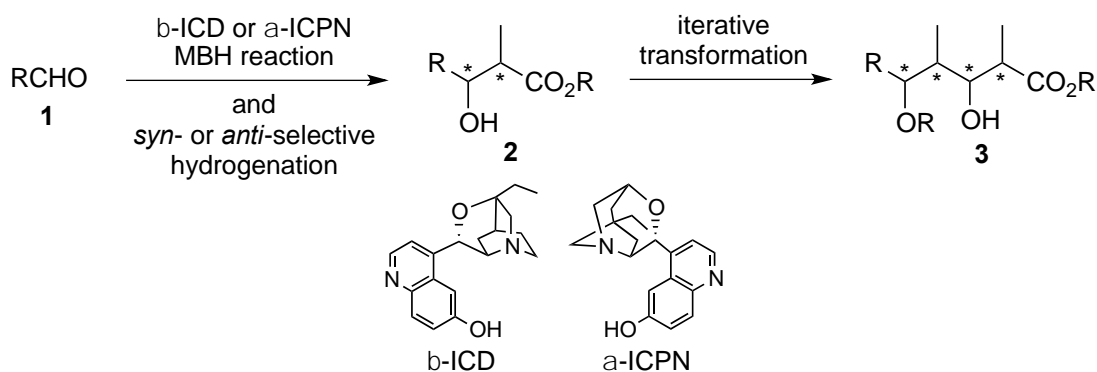
## SYNTHETIC STUDY OF THERMOLIDES: STEREOSELECTIVE CONSTRUCTION OF THE C10-C21 FRAGMENT

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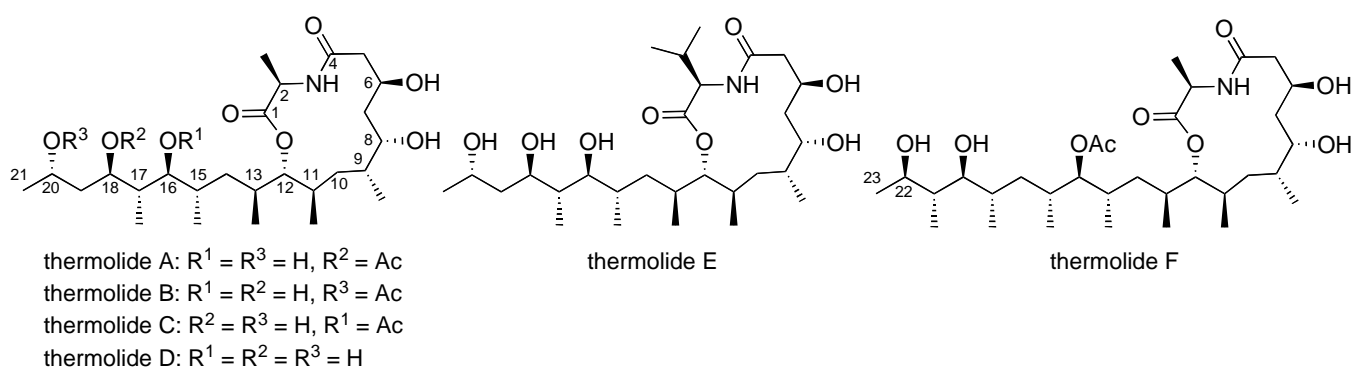
**Abstract** – The C10-C21 fragment of nematocidal thermolides, macrocyclic PKS-NRPS hybrid metabolites isolated from a thermophilic fungus, was prepared in a highly stereoselective manner. The stereocontrol was accomplished by taking advantage of a cinchona alkaloid-catalyzed Morita-Baylis-Hillman reaction followed by diastereoselective hydrogenation and a cinchona alkaloid-catalyzed asymmetric  $\beta$ -lactone formation.

Recently, we have developed an enantio- and diastereoselective method for the synthesis of a  $\beta$ -methyl- $\gamma$ -hydroxy ester **2** from an aldehyde **1** in catalyst-controlled manner, which involves a cinchona alkaloid-catalyzed asymmetric Morita-Baylis-Hillman reaction<sup>1</sup> and subsequent *syn*- or *anti*-selective hydrogenation. The iterative use of this transformation allowed us to construct all possible stereoisomers of a polypropionate stereotetrad **3** having four contiguous stereogenic centers (Scheme 1).<sup>2</sup> In addition, we have achieved asymmetric syntheses of tirandamycin family of antibiotics utilizing this methodology.<sup>3</sup> To further demonstrate the synthetic utility, we became interested in the synthesis of the thermolides.



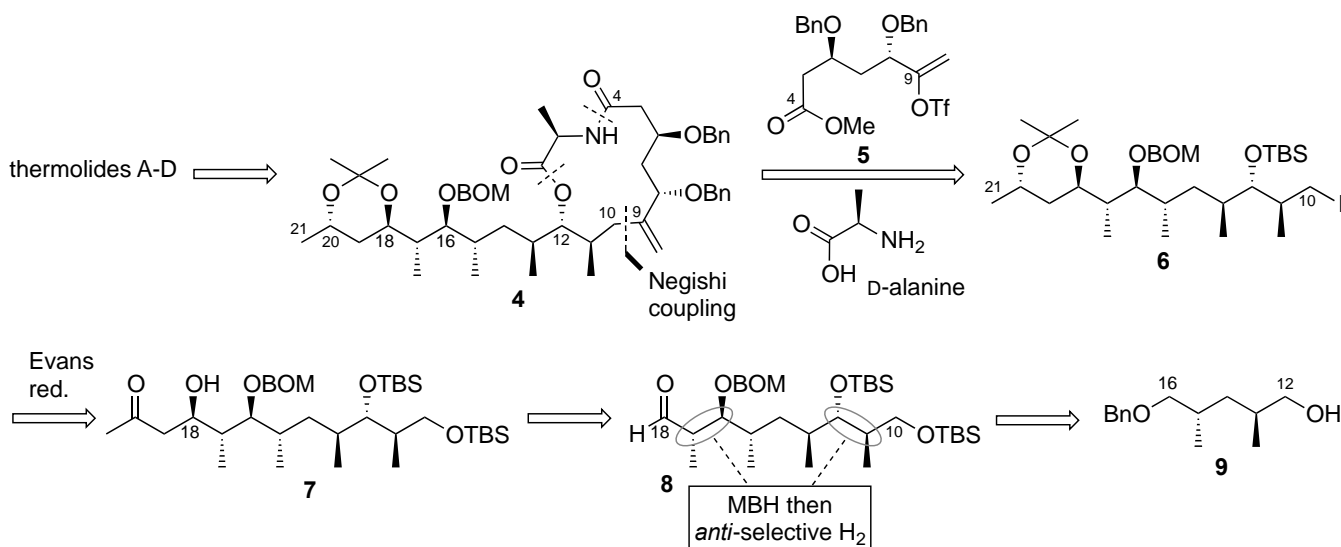
**Scheme 1.** Polypropionate synthesis based on asymmetric MBH reactions

In 2012, Zhag and Niu et al. reported the isolation of thermolides A-F from the culture broths of a thermophilic fungus *Talaromyces thermophilus* (Figure 1).<sup>4,5</sup> These compounds belong to macrocyclic PKS-NRPS hybrid metabolites and possess characteristic mixed polyketide/amino acid structures containing a 13-membered lactam bearing macrolactone. Interestingly, thermolides A and B exhibited potent inhibitory activities against three notorious nematodes ( $LC_{50} = 0.5-1 \mu\text{g/mL}$ ), which are to those of avermectins ( $LC_{50} = 0.5-0.8 \mu\text{g/mL}$ ). The intriguing biological activities and molecular architectures make the thermolides good targets for synthesis; however, even the synthetic studies have to be reported. We herein report the highly enantio- and diastereoselective synthesis of the C10-C21 fragment.



**Figure 1.** Thermolides A-F

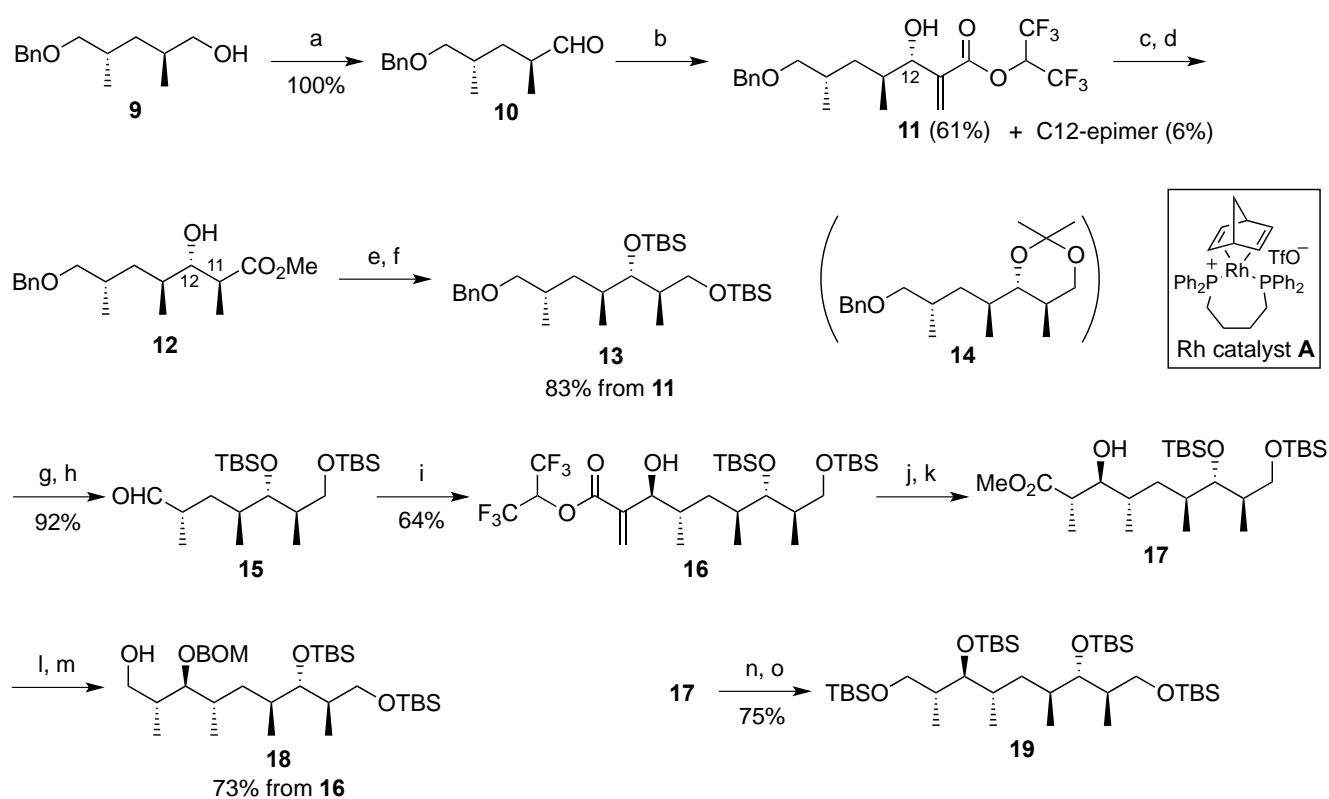
Retrosynthetically, we envisioned **4** as a common precursor of thermolides A-D, from which site selective acetylation of C16, C18, or C20 hydroxy group and stereoselective hydrogenation of C9 methylene would be possible (Scheme 2). To access **4** we envisioned a convergent approach through Negishi coupling<sup>6,7</sup> of C10-C21 fragment **6** with C4-C9 fragment **5**, amidation, and macrolactonization.



**Scheme 2.** Retrosynthetic analysis of thermolides

The synthesis of **6**, the topic of this report, would be realized from **8** through stereoselective formation of  $\beta$ -hydroxy ketone **7** and Evans' *anti*-selective reduction.<sup>8</sup> The aldehyde **8** could, in turn, be stereoselectively accessed from known chiral building block **9**<sup>9</sup> by taking advantage of our methodology shown in Scheme 1.

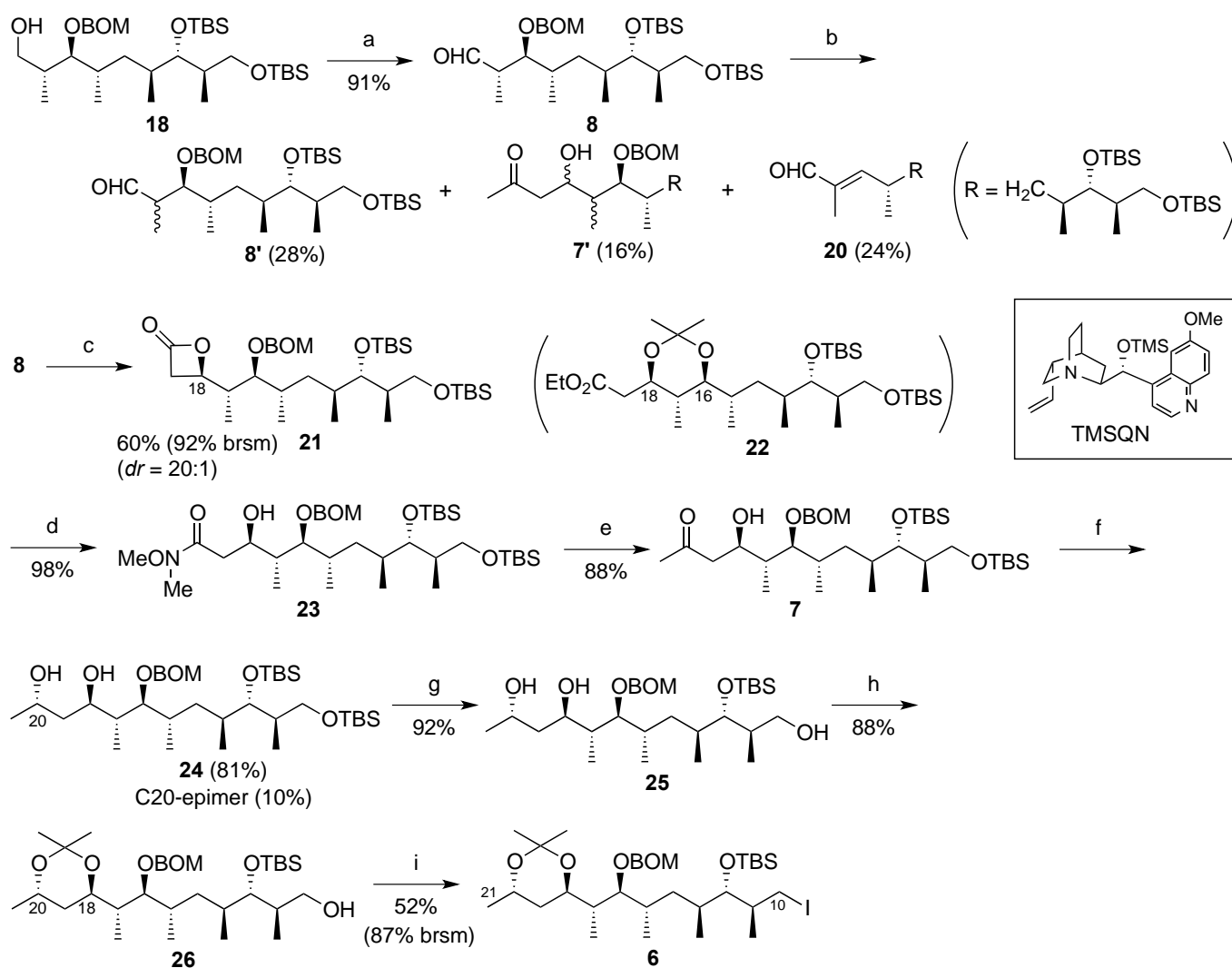
The synthesis of C10-C21 fragment **6** began with  $\alpha$ -isocupreine ( $\alpha$ -ICPN)-catalyzed MBH reaction of aldehyde **10**, prepared by Swern oxidation of enantiomerically pure alcohol **9**,<sup>9</sup> with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) (Scheme 3). The reaction was conducted using 0.3 equiv of  $\alpha$ -ICPN and 4 equiv of HFIPA in DMF at  $-55$  °C and MBH adduct **11** was obtained in 61% yield together with the corresponding C12-epimer (6%).<sup>10</sup> It is important to note that when the MBH reaction was undertaken employing  $\beta$ -isocupreidine ( $\beta$ -ICD) in place of  $\alpha$ -ICPN under the same conditions, the C12-epimer was obtained as a single diastereomer in 61% yield. Upon methanolysis and hydrogenation under the conditions using 0.04 equiv of rhodium catalyst **A**,<sup>11</sup> compound **11** afforded **12** in excellent *anti*-selectivity. The absolute configuration of the C12 position was determined to be *S* by the modified Mosher's method.<sup>12</sup> The 11,12-*anti* stereochemistry was confirmed by the NOESY spectrum of acetonide **14** derived from **12** by  $\text{LiAlH}_4$  reduction followed by acetonidation.



**Scheme 3.** Reagents and conditions: (a)  $(\text{COCl})_2$ , DMSO,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78$  °C to rt; (b)  $\alpha$ -ICPN (0.3 equiv), HFIPA (4 equiv), DMF,  $-55$  °C; (c) MeOH,  $\text{NaHCO}_3$ ; (d) Rh catalyst **A** (0.04 equiv),  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; (e)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0$  °C; (f) TBSOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $0$  °C; (g)  $\text{H}_2$ , Pd/C, AcOEt; (h) DMPI,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (i)  $\alpha$ -ICPN (0.3 equiv), HFIPA (4 equiv), DMF,  $-55$  °C; (j) MeOH,  $\text{NaHCO}_3$ ; (k) Rh catalyst **A** (0.04 equiv),  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; (l) BOMCl,  $i\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , reflux; (m)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0$  °C; (n)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0$  °C; (o) TBSOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $0$  °C.

The crude **12** obtained from **11** was then subjected to  $\text{LiAlH}_4$  reduction followed by silylation to give **13** in 83% yield over 4 steps. Successive debenzoylation and Dess-Martin oxidation converted **13** to **15** in 92% yield. The aldehyde **15** was again subjected to  $\alpha$ -ICPN-catalyzed MBH reaction with HFIPA under the same conditions as those employed for the conversion of **10** to **11** and MBH adduct **16** was obtained as a single diastereomer in 64% yield. Compound **16** was then converted to **18** via **17** by a four step-sequence involving methanolysis, rhodium-catalyzed *anti*-selective hydrogenation,<sup>11</sup> protection as a benzyloxymethyl (BOM) ether, and  $\text{LiAlH}_4$  reduction in 73% overall yield. The stereochemistry of **17** was confirmed by its conversion to C2 symmetrical tetra-TBS ether **19** by  $\text{LiAlH}_4$  reduction followed by silylation.

To obtain  $\beta$ -hydroxy ketone **7**, we first examined L-proline-catalyzed cross aldol reaction<sup>13</sup> of aldehyde **8** with acetone (Scheme 4). Thus, alcohol **18** was oxidized to **8** in 91% yield, which was reacted with acetone in the presence of L-proline (0.3 equiv) in  $\text{DMSO-CHCl}_3$  (1:1) at room temperature.



**Scheme 4.** Reagents and conditions: (a) DMPI,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (b) L-proline (0.3 equiv),  $\text{DMSO-CH}_2\text{Cl}_2$  (1:1), 8 days; (c) TMSQN (0.2 equiv),  $\text{LiClO}_4$  (4 equiv),  $\text{AcCl}$ ,  $i\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; (d)  $\text{NHMe(OMe)\cdot HCl}$ ,  $\text{Et}_2\text{AlCl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (e)  $\text{MeLi}$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ ; (f)  $\text{NMe}_4\text{BH(OAc)}_3$ ,  $\text{AcOH}$ ,  $\text{MeCN}$ ,  $-20^\circ\text{C}$ ; (g)  $\text{CSA}$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ ; (h)  $\text{Me}_2\text{C(OMe)}_2$ , PPTS, acetone, then PPTS,  $\text{EtOH}$ ; (i)  $\text{I}_2$ ,  $\text{PPh}_3$ , imidazole,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt.

However, the reaction was very sluggish to give a complex mixture including diastereoisomeric  $\beta$ -hydroxy ketone **7'** (16%),  $\alpha,\beta$ -unsaturated aldehyde **20** (24%), and epimerized starting aldehyde **8'** (28%). With this failure, we then investigated an alternative approach via a cinchona alkaloid-catalyzed cyclocondensation reaction.<sup>14</sup> When aldehyde **8** was reacted with acetyl chloride using 0.2 equiv of TMSQN and 4 equiv of LiClO<sub>4</sub> at  $-78$  °C according to Nelson's protocol,<sup>14</sup> the reaction was proceeded with excellent diastereoselectivity ( $dr = 20:1$ ) and  $\beta$ -lactone **21** was obtained in 60% yield (92% brsm).<sup>15</sup> The stereochemistry of the C18 position was determined by applying Rychnovsky's method<sup>16</sup> to acetonide **22** derived from **21** by sequential ethanolysis, hydrogenolytic removal of the BOM group, and acetonidation. Compound **21** was then converted to the desired  $\beta$ -hydroxy ketone **7** via Weinreb amide **23** in 86% yield.<sup>17</sup>  $\beta$ -Hydroxy ketone **7**, thus obtained, was subjected to Evans' *anti*-selective reduction<sup>8</sup> to give diol **24** and its C20-epimer in 81% and 10% yields, respectively. After selective desilylation of the primary TBS ether of **24**, the resulting triol **25** was converted to acetonide **26** by acetonidation followed by cleavage of the resulting mixed acetal of the primary alcohol. The stereochemistry of the C20 position of **26** was clearly determined by Rychnovsky's method.<sup>16</sup> Finally, iodination of **26** allowed us to obtain the objective C10-C21 fragment **6** in 52% yield.

In conclusion, we have developed a highly enantio- and diastereoselective approach to the C10-C21 fragment **6** via a cinchona alkaloid-catalyzed asymmetric MBH reaction followed by a rhodium-catalyzed *anti*-selective hydrogenation and a cinchona alkaloid-catalyzed cyclocondensation reaction. The synthesis of thermolides along the retrosynthetic analysis shown in Scheme 2 is under progress in our laboratory.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

<sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds are available.

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