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Stereoselective Synthesis of Tetrahydrofuran Lignans via BF_3·OEt_2-Promoted Reductive Deoxygenation/Epimerization of Cyclic Hemiketal: Synthesis of (–)-Odoratisol C, (–)-Futokadsurin A, (–)-Veraguensin, (+)-Fragransin A_2, (+)-Galbelgin, and (+)-Talaumidin

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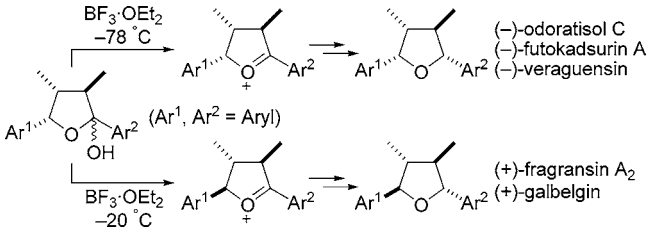
ABSTRACT



A versatile route to the synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans, (–)-odoratisol C (1), (–)-futokadsurin A (2), (–)-veraguensin (3), (+)-fragransin A_2 (4), (+)-galbelgin (5), and (+)-talaumidin (6), is described. Central to the synthesis of the lignans is BF_3·OEt_2-promoted deoxygenation/epimerization of the hemiketal 9a followed by stereoselective reduction of the oxocarbenium ion intermediates 8a,b.

Lignans and neolignans are a class of secondary plant metabolites produced by oxidative dimerization of two phenylpropane (C6−C3) units, which are formed biogenetically through the shikimate pathway.[1] Although their molecular backbone consists of only two phenylpropane units, lignans show an enormous structural diversity. Lignans possess significant pharmacological activities, including antitumor, anti-inflammatory, immunosuppressive, cardiovascular, neuroprotective, neurotrophic, antioxidant, and antiviral actions.[2] There is a growing interest in lignans and their synthetic derivatives due to applications in cancer chemotherapy and a variety of other pharmacological effects. Among lignans and neolignans, 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans have stimulated substantial synthetic efforts due to their structural diversity and biological activity.[3]

Herein, we report a versatile route to the synthesis of (−)-odoratisol C (**1**),[4] (−)-futokadsurin A (**2**),[5] (−)-veraguensin (**3**),[6] (+)-fragransin A_2 (**4**),[7] (+)-galbelgin (**5**),[8] and (+)-

(1) (a) Whiting, D. A. *Nat. Prod. Rep.* **1990**, *7*, 349. (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75 and references cited therein.

(2) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696.

(3) (a) Hanessian, S.; Reddy, G. J. *Synlett*. **2007**, 475. (b) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477. (c) Esumi, T.; Hojyo, D.; Zhai, H.; Fukuyama, Y. *Tetrahedron Lett.* **2006**, *47*, 3979. (d) Jahn, U.; Rudakov, D. *Org. Lett.* **2006**, *8*, 4481 and references cited therein.

(4) Giang, P. M.; Son, P. T.; Matsunami, K.; Otsuka, H. *Chem. Pharm. Bull.* **2006**, *54*, 380.

(5) Konishi, T.; Konoshima, T.; Daikonya, A.; Kitanaka, S. *Chem. Pharm. Bull.* **2005**, *53*, 121.

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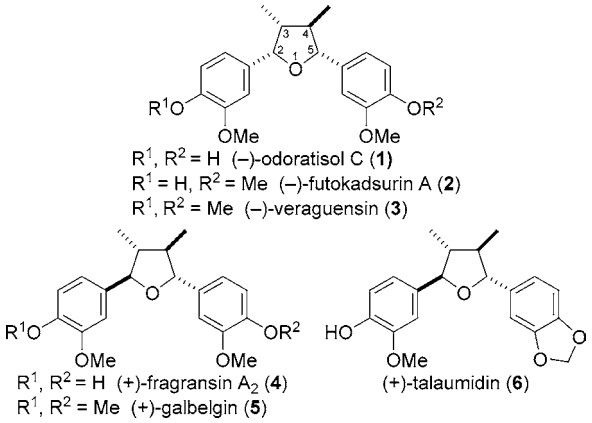
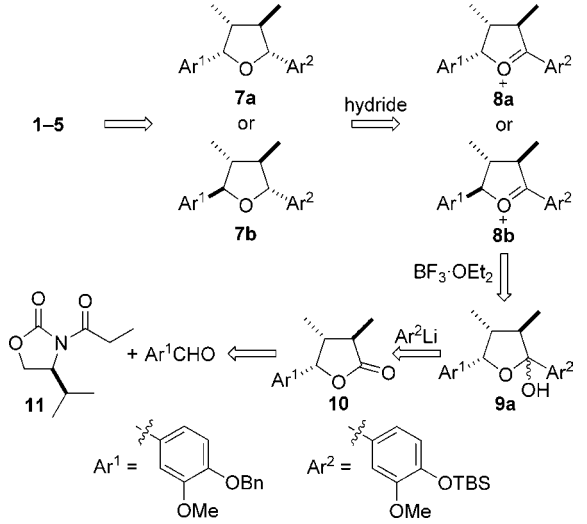


Figure 1. 2,5-Diaryl-3,4-dimethyltetrahydrofuran lignans.

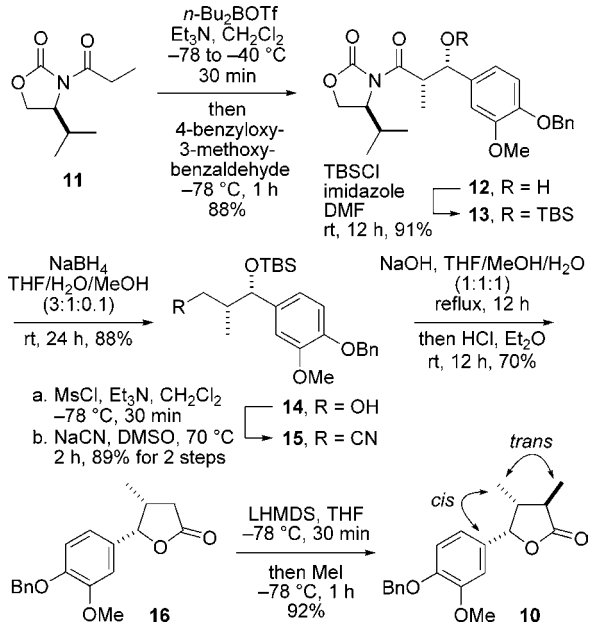
talaumidin (**6**)[9] (Figure 1) via BF_3·OEt_2-promoted deoxygenation/epimerization of the hemiketal **9a** followed by stereoselective reduction of the oxocarbenium ion intermediates **8a**,**b**.

Scheme 1. Retrosynthetic Analysis



Scheme 1 describes our approach to the synthesis of tetrahydrofuran lignans (**1**−**5**) via 3,4-dimethyl-5-aryldihydrofuran-2(3*H*)-one (**10**), which could be constructed by employing the highly stereoselective Evans asymmetric *syn*-aldol reaction of (4*S*)-4-(1-methylethyl)-3-(1-oxopropyl)-2-oxazolidinone (**11**) with 4-benzyloxy-3-methoxybenzaldehyde. The strategy underlying our synthetic plan was to apply nucleophilic addition of an aryllithium reagent to **10** followed by stereoselective reduction of the oxocarbenium ion intermediate **8a** formed from BF_3·OEt_2-promoted deoxygenation of the cyclic hemiketal **9a**. We anticipated a hydride to be added to **8a** from the inside face of the envelope conformer to stereoselectively provide the 2,3-*cis*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **7a** for the synthesis of (−)-odoratisol C (**1**), (−)-futokadsurin A (**2**), and (−)-veraguensin (**3**). In addition, we expected that BF_3·OEt_2-promoted epimerization of the hemiketal **9a** followed by reductive deoxygenation to produce **7b** would complete the synthesis of (+)-fragransin A_2 (**4**) and (+)-galbelgin (**5**).

Scheme 2. Synthesis of 3,4-Dimethyl-5-aryldihydrofuran-2(3*H*)-one (**10**)



As outlined in Scheme 2, the synthesis of 3,4-dimethyl-5-aryldihydrofuran-2(3*H*)-one (**10**) began with the highly stereoselective Evans asymmetric *syn*-adol reaction.[10] Commercially available 4-benzyloxy-3-methoxybenzaldehyde was reacted with (4*S*)-4-(1-methylethyl)-3-(1-oxopropyl)-2-oxazolidinone (**11**) in the presence of *n*-Bu_2BOTf and Et_3N to provide the desired *syn*-adol adduct **12** in 88% yield as a single diastereomer. Protection of **12** with TBSCl (91%) followed by reduction of **13** with $NaBH_4$ provided the corresponding alcohol **14** (88%). Protection of **14** with MsCl and subsequent treatment with NaCN accomplished one-carbon homologation to give **15** (89% for two steps). Single-step conversion of **15** to the γ-lactone **16** was achieved by treatment with NaOH in refluxing THF/MeOH/H_2O followed by acidic workup with HCl in Et_2O (70%). Stereocontrolled α-methylation of the γ-lactone **16** under conventional conditions (LHMDS, MeI) exclusively produced 3,4-dimethyl-5-aryldihydrofuran-2(3*H*)-one (**10**) in 92% yield.

(6) Crossley, N. S.; Djerassi, C. *J. Chem. Soc.* **1962**, 1459.

(7) (a) Hattori, M.; Hada, S.; Kawata, Y.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Chem. Pharm. Bull.* **1987**, *35*, 3315. (b) Hanessian et al. established the correct absolute configuration of (+)-fragransin A_2; see ref 3a.

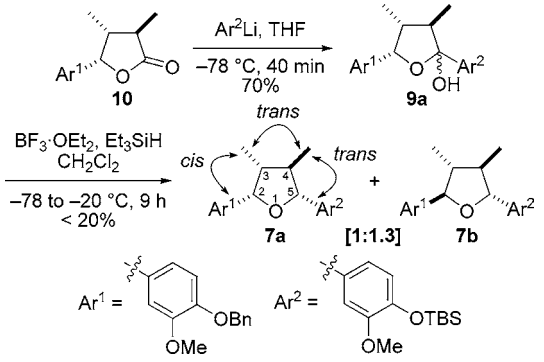
(8) (a) Takaoka, D.; Watanabe, K.; Hiroi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3564. (b) Hanessian et al. confirmed the stereochemical assignment of (+)-galbelgin; see ref 3a.

(9) Zhai, H.; Nakatsukasa, M.; Mitsumoto, Y.; Fukuyama, Y. *Planta Med.* **2004**, *70*, 598.

(10) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) For a similar Evans aldol strategy for the synthesis of a stereoisomer of **14**, see ref 3c.

Next, we converted **10** into the 2,3-*cis*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **7a** (Scheme 3). Treatment of **10** with 4-*tert*-butyldimethylsilyloxy-3-methoxyphenyllithium gave a 4:1 anomeric mixture of the cyclic hemiketal **9a** in 70% yield (86% based on recovered starting material). We expected that treatment of **9a** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$[11] would preferentially provide the 2,3-*cis*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **7a** through the addition of hydride from the inside face of the envelope conformer (vide infra). However, the reaction conditions for reductive deoxygenation ($BF_3{\cdot}OEt_2$, Et_3SiH, −78 to −20 °C, 9 h) gave a 1.3:1 diastereomeric mixture of 2,5-diaryl-3,4-dimethyltetrahydrofurans in poor yield (<20%). To our surprise, careful analysis of ^1H NMR spectral data revealed that the major diastereomer had the 2,3-*trans*-3,4-*trans*-4,5-*trans*-configuration **7b** and the minor diastereomer had the desired 2,3-*cis*-3,4-*trans*-4,5-*trans*-configuration **7a**, indicating that epimerization of the C2-aryl group occurred under the reaction conditions.[12]

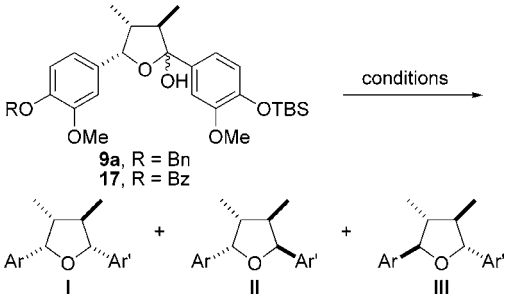
Scheme 3. Reductive Deoxygenation of Cyclic Hemiketal **9a**



The observed epimerization of **9a** was rationalized on the basis that Lewis acid activation of the hemiketal **9a** by $BF_3{\cdot}OEt_2$ combined with an inductive effect of the electron-donating Bn group on the C2-aryl substituent effectively competed with slow reduction of the oxocarbenium ion intermediate **8a** by Et_3SiH.[13] On the basis of this rationale, we expected that either fast reduction of **8a** or a change of the electron-donating Bn group on the aryl substituent to an electron-withdrawing group would prevent the epimerization of the C2-aryl group.[14]

Table 1 summarizes the stereoselectivity of the reductive deoxygenation reaction of **9a**. When **9a** was treated with $BF_3{\cdot}OEt_2$ combined with $NaBH_3CN$ (a strong reducing agent), the reaction proceeded to give a 10:1 diastereomeric mixture of **9a-I** and **9a-II** (99%) without epimerization of the C2-aryl group (entry 1). In the case of the electron-withdrawing Bz protecting group on the C2-aryl substituent, the reductive deoxygenation reaction of **17**[15] ($BF_3{\cdot}OEt_2$, Et_3SiH, −78 to −20 °C, 3 h) also proceeded without epimerization of the C2-aryl group to give **17-I** in excellent diastereoselectivity (**17-I**:**17-II** = 25:1, 62%) (entry 2). However, epimerization of **9a**, afforded by treatment with $BF_3{\cdot}OEt_2$ (−78 to −20 °C, 2 h), followed by reduction with $NaBH_3CN$ provided a 1:0.1:4 mixture of **9a-I**, **9a-II**, and **9a-III** (96%) (entry 3).

Table 1. Stereoselectivity of the Reductive Deoxygenation Reaction



entry	substrate	conditions	ratio (**I**:**II**:**III**)
1	**9a**	$BF_3{\cdot}OEt_2$, $NaBH_3CN$, −78 °C, 30 min	10:1:0
2	**17**	$BF_3{\cdot}OEt_2$, Et_3SiH, −78 to −20 °C, 3 h	25:1:0
3	**9a**	$BF_3{\cdot}OEt_2$, −78 to −20 °C, 2 h then $NaBH_3CN$, −78 °C, 30 min	1:0.1:4

Treatment of **9a** with $BF_3{\cdot}OEt_2$ (−78 to −20 °C, 2 h) in the absence of a reducing agent resulted in an equilibrium between **9a** and **9b** (1:4 ratio) proving the observed $BF_3{\cdot}OEt_2$-promoted epimerization of **9a** (Scheme 4). The epimerization of **9a** might occur through a quinonoid oxonium ion intermediate facilitated by an inductive effect of the electron-donating Bn group on the C2-aryl substituent.[3a,b,13] Further study is required to prove the putative mechanism. The preference for **9b** in equilibrium can be explained by unfavorable steric interaction between *cis* substituents in **9a**. To determine the stereochemical outcome of hydride reduction, we isolated and independently subjected **9a** and **9b** to reductive deoxygenation conditions ($BF_3{\cdot}OEt_2$, $NaBH_3CN$, −78 °C, 30 min). Under the reaction conditions, **9a** and **9b** provided **7a** (**7a**:**7c** = 10:1, 99%) and **7b** (single diastereomer, 92%), respectively.[16] The stereochemical outcome can be explained by Woerpel's recent studies.[17] Due to unfavorable steric interactions of the incoming hydride with axially oriented 3,4-dimethyl groups in conformation **A**, the hydride adds to the sterically more favorable conformation **B** from

(11) Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 679.

(12) It is known that 2,5-diaryl-3,4-*trans*-dimethyltetrahydrofurans have unique chemical shifts for H2, H3, H4, and H5 in ^1H NMR depending on their relative stereochemistry. Thus, we determined the relative stereochemistry of tetrahydrofurans **7a** and **7b** by comparison of chemical shifts in ^1H NMR with literature values; see refs 3−9.

(13) For an example of Lewis acid-mediated fragmentation/isomerization of furofurans, see: Aldous, D. J.; Dalencon, A. J.; Steel, P. G. *J. Org. Chem.* **2003**, *68*, 9159.

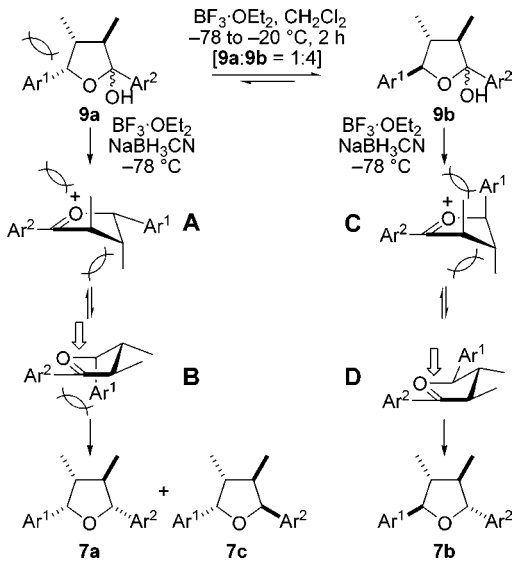
(14) Hanessian et al. reported a method for the stereocontrolled synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans by modulating the nature of a directing para substituent on one of the aryl groups; see refs 3a and 3b.

(15) **17** was prepared from **10** by Bn-deprotection, Bz-protection, and ArLi-addition; see the Supporting Information for details.

(16) It is important to note that the *cis*,*trans*-hemiketal **9a** and *trans*,*trans*-hemiketal **9b** are both configurationally stable under the reaction condition.

(17) (a) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149. (b) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056. (c) Larsen, C. H.; Riggway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (d) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747. (e) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706.

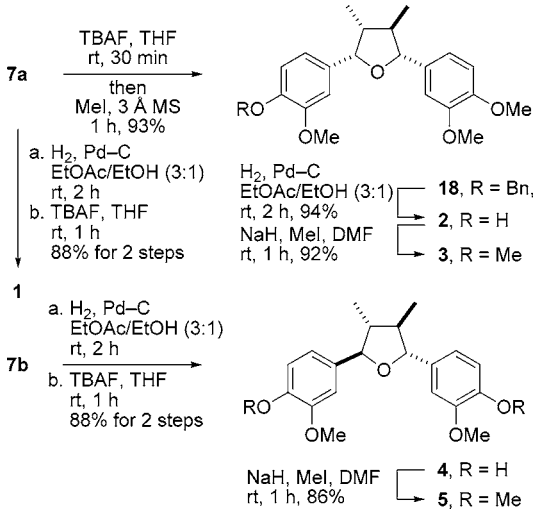
Scheme 4. $BF_3{\cdot}OEt_2$-Promoted Epimerization and Reductive Deoxygenation



the inside face of the envelope conformer ("inside attack" model) to provide the desired 2,3-*cis*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **7a**. Also, in the case of **9b**, 2,3-*trans*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **7b** was formed from comformation **D** via "inside attack" of the hydride.

With both **7a** and **7b** in hand, we proceeded to complete the synthesis of tetrahydrofuran lignans **1**−**5** (Scheme 5).

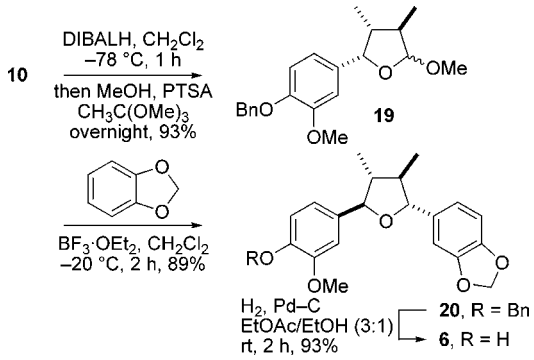
Scheme 5. Synthesis of Tetrahydrofuran Lignans **1**−**5**



Deprotection of TBS and Bn groups under conventional conditions converted **7a** to (−)-odoratisol C (**1**) (88% for two steps). One-pot TBS-deprotection/methylation of **7a** provided **18** (93%), and subsequent removal of the Bn protecting group in **18** with H_2/Pd-C afforded (−)-futokadsurin A (**2**) (94%). Synthesis of (−)-veraguensin (**3**) was achieved by methylation of **2** in 92% yield. Removal of TBS and Bn protecting groups in **7b** gave (+)-fragransin A_2 (**4**) (88% for two steps) and methylation of **4** completed the synthesis of (+)-galbelgin (**5**) (86%).

The epimerization of the C2-aryl group was also utilized in the synthesis of (+)-talaumidin (**6**) (Scheme 6). The

Scheme 6. Synthesis of (+)-Talaumidin (**6**)



lactone **10** was converted to the methyl acetal **19** through one-pot reduction (DIBALH) and acetalization in 93% yield. As we expected, Friedel−Crafts-type arylation conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to −20 °C, 2 h)[3c] proceeded with the epimerization at the C2 position of **19** to provide 2,3-*trans*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **20** as a single diastereomer (89%). Final deprotection of the Bn protecting group in **20** completed the synthesis of (+)-talaumidin (**6**) (93%).

In summary, we applied $BF_3{\cdot}OEt_2$-promoted deoxygenation/epimerization of the cyclic hemiketal **9a** and stereoselective reduction of the oxocarbenium ion intermediates **8a**,**b** to the synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans. Combination of $BF_3{\cdot}OEt_2$ with a strong reducing agent (e.g., $NaBH_3CN$) enabled the synthesis of (−)-odoratisol C (**1**), (−)-futokadsurin A (**2**), and (−)-veraguensin (**3**) without epimerization of the C2-aryl group, whereas $BF_3{\cdot}OEt_2$-promoted epimerization of **9a** or methyl acetal **19** under the conditions of slow reduction (e.g., Et_3SiH) combined with an electron-donating protecting group (e.g., Bn) was explored for the synthesis of (+)-fragransin A_2 (**4**), (+)-galbelgin (**5**), and (+)-talaumidin (**6**). This versatile synthetic strategy should be broadly applicable to the efficient synthesis of a diverse set of bioactive 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans.

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Supporting Information Available: General experimental procedures including spectroscopic and analytical data for compounds **1**−**7**, **9**, **10**, and **12**−**20** along with copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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