Substituted Dineolignans from *Magnolia garrettii*

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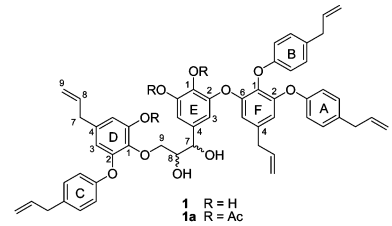
In the course of a study on lignan profiles of tropical and subtropical members of the Magnoliaceae, *Magnolia garrettii*, an evergreen tree known from northern Thailand, Vietnam, and southern Yunnan (China), was investigated. The work resulted in the isolation of two dimeric lignans from the dichloromethane extract of the leaves of *M. garrettii*, garrettilignan A (**1**) and garrettilignan B (**2**), each substituted with two additional *p*-allylphenolic moieties. Garrettilignans A (**1**) and B (**2**) represent new skeletal types within the neolignan class. Additionally, four known neolignans, magnolol, honokiol, 4′-methylhonokiol, and obovatol, were identified.

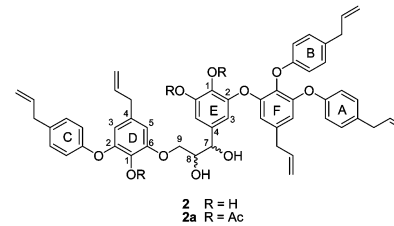
Magnoliaceae has a major center of diversification in southeastern Asia. *Magnolia garrettii* (Craib) V.S. Kumar (= *Manglietia garrettii* Craib) (Thai name *montha doi*, *montha pa*) is a medium-sized tree native to montane seasonally dry forests of mainly northern Thailand, but also in Vietnam and the southern Yunnan Province of China.[1−3] The evergreen tree reaches up to 30 m in height, its leaves are coriaceous and narrowly elliptic, and its dark pink flowers are considered to display the strongest coloration of all Magnoliaceae flowers.[3−6] The taxonomic rank of the genus *Manglietia* has been a source of controversy, and strong arguments on the basis of data from molecular analyses as well as from detailed morphological inspection have been brought to merge the genus *Manglietia* into *Magnolia*.[7−11] However, previous scientific literature and the taxonomic treatment in the *Flora of China*[4] refer mostly to the separate genus *Manglietia*, which is now considered a section of *Magnolia*.[11]

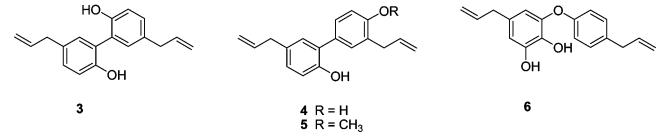
Reports on the chemical constituents of *Magnolia*, section *Manglietia*, of which ca. 24 species are native to Thailand, are still scant. *Magnolia phuthoensis* (Dandy ex. Gagnep.) V.S. Kumar (= *Manglietia phuthoensis* Dandy ex. Gagnep.) from Vietnam was reported to contain lignan glycosides, i.e., mangliesides, together with known neolignans such as obovatol and 3-methoxymagnolol.[12] Other studies reported the isolation of a dibenzopyrrocoline alkaloid from *M. conifera* var. *chingii* (Dandy) V.S. Kumar (= *M. chingii* Dandy)[13] and on the occurrence of biphenyl-type neolignans as well as the sesquiterpene lactone costunolide in the stem bark of *M. garrettii*.[14] Reports on the medicinal use of *M. garrettii* could not been found in western literature. However, it is possible that its bark is used as a substitute for the important medicinally used bark of *Magnolia officinalis* (Magnoliae cortex, Hou-Po) from China.

Results and Discussion

The phytochemical investigation of the dichloromethane extract of the leaves from *M. garrettii* led to the isolation of the four known neolignans magnolol (**3**), honokiol (**4**), 4′-methylhonokiol (**5**), and obovatol (**6**) together with two new dimeric substituted neolignans, garrettilignans A (**1**) and B (**2**). Extensive NMR and MS analyses of the isolated compounds and their acetylated derivatives (**1a** and **2a**) allowed the unambigous structural assignment of these two neolignan derivatives.







Compound **1** was isolated as a light brown, amorphous matter. The positive HR-ESIMS of **1** showed a pseudomolecular ion peak at *m*/*z* 865.3418, corresponding to $[M - H_2O + Na]^+$ and suggesting a molecular formula of $C_{54}H_{52}O_{10}$ (calcd *m*/*z* 860.3560). The ^1H and ^{13}C NMR spectra indicated the presence of six phenylpropanoid units. Resonance assignments for their spin systems in DQF-COSY, HSQC, and HMBC revealed the presence of three 4-allylphenol subunits (subunits A, B, and C), two 4-allyl-1,2,6-trihydroxyphenyl subunits (subunits D and F), and a 4-trihydroxypropyl-1,2,6-trihydroxyphenyl subunit (subunit E). The presence of six ^{13}C and two ^1H NMR shift values for the six phenyl carbons and two aromatic hydrogens of subunits D−F required an asymmetric substitution pattern in these rings. An HMBC coupling between H-9 of subunit E and C-1 of subunit D supported the covalent linkage between these subunits, whereas no further HMBC correlations between any of the other subunits could be detected, which suggested the presence of an aryl ether linkage between the other subunits. To determine the position of these linkages, data from NMR and particularly selective NOE experiments using the triacetylated garrettilignan A (**1a**), which showed a better dispersion of proton resonances compared to the nonacetylated garrettilignan (**1**), were examined. NMR data and a molecular ion in the positive ESIMS at *m*/*z* 991.4 corresponding to $[M - H_2O + Na]^+$ indicated the presence of three acetyl groups in **1a**. As a rule of thumb, acetylation leads to a ^{13}C NMR high-field shift of ∼4 ppm for the

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ipso position and a low-field shift of ~6 ppm for the *ortho* and *para* positions. Such changes found in carbon NMR shift values indicated the acetylation at C-6 in subsystem D together with C-1 and C-6 in subsystem E (see Table 1). Selective inversion of the proton resonance H-2/6 in subunit C led to an observed NOE interaction with H-3 of subunit D, therefore supporting the attachment of subunit C to subunit D at C-2 via an aryl ether linkage. Similarly, selective inversion of the H-3 resonance in subunit F led to an NOE for H-2/6 of subunit A, thus supporting the attachment of subunit A to C-2 in subunit F. The experimental results from acetylation as well as from NOE observations narrowed the number of possible structures down to two, i.e., a structure with an attachment of subunit E to C-1 or C-6 of subunit F, respectively. The remaining C-1 or C-6 positions of subunit F, respectively, are linked further to subunit B. Taking into account that subunit F must be substituted nonsymmetrically, the only possible attachment point for subunit E is that to C-6 in subunit F. This assignment was further corroborated by a weak NOE signal observed between H-5 of subunit F and H-3 of subunit E. Therefore, the structure of garrettilignan A (**1**) was assigned as shown.

The molecular formula and the number of phenylpropanoids units indicate the presence of a trimeric neolignan. From a biosynthetic point of view, however, only subunits C and D, as well as E and F, respectively, each resemble the known neolignan obovatol due to the oxidation pattern of the phenolic ring and the ether linkage. Hence, garrettilignan A (**1**) is most adequately described as a substituted dineolignan bearing two additional 4-allylphenol moieties (A and B) attached to subunit F. The relative configuration of C-7 and C-8 of the propyl chain of subsystem E could not be assigned in compound **1**. The ^{1}H and ^{13}C NMR chemical shifts for compounds **1** and **1a** are presented in Table 1.

Compound **2** showed an ion peak of *m/z* 865.3418 [M − H_2O + Na]$^+$ using positive-mode HR-ESIMS, indicating a molecular formula of $C_{54}H_{52}O_{10}$ (calcd *m/z* 860.3560). As in compound **1**, ^{1}H and ^{13}C NMR spectra indicated the presence of six phenylpropanoid units, suggesting an isomer of **1**. Spin system assignments based on DQF-COSY, HSQC, and HMBC experiments revealed the presence of three 4-allylphenol subunits (A−C), two 4-allyl-1,2,6-trihydroxyphenol subunits (D and F), and one 4-trihydroxypropyl-1,2,6-trihydroxyphenol subunit (E). As with compound **1**, nonsymmetric substitution patterns in rings D−F of **2** were concluded from the observation of six ^{13}C and two ^{1}H NMR shift values. HMBC correlations between H-9 in subunit E and C-6 of subunit D proved the linkage of these subunits. Selective inversion of proton resonance H-3 in subunit D led to an observed NOE for H-2/6 of subunit C, therefore indicating an attachment of subunit C to subunit D at C-2 via an aryl ether linkage. Selective inversion of H-3 of subunit F led to NOE signals for H-2/6 in subunit A, thus indicating the attachment of subunit A to C-2 in subunit F. In addition, an NOE signal was observed between H-5 in subunit F and H-3 in subunit E. To further elucidate the linkage position for the different subunits, the phenolic hydroxy positions were acetylated, resulting in triacetylated compound **2a**, as could be verified by the presence of three acetyl signals in ^{1}H and ^{13}C NMR spectra. Differences between the triacetylated compounds **1a** and **2a** were only seen in the ^{13}C shift values of rings D and E (Table 1). In comparison to the signals found in compound **1a**, differences in acetylation shifts were only found in ring D, corroborating also the HMBC correlation between subunits E and D. In conclusion, the difference between the two isomeric compounds **1** and **2** was found to lie in the different linkage between subunits E and D; that is, the obovatol moiety comprising subunits D and C is attached via position C-6 to the trihydroxypropyl chain of subunit E in compound **2**, whereas it is attached via position C-1 in compound **1**. Taking these informations together, garrettilignan B (**2**) was assigned as shown. The ^{1}H and ^{13}C NMR chemical shift data for compounds **2** and **2a** are presented in Table 1.

Di- and trimeric lignans and neolignans are rare natural compounds. Besides occurring in gymnosperms, dilignans have been occasionally found, for example, in Aizoaceae, Asteraceae, Leguminosae, Myristicaceae, Rubiaceae, and Saururaceae,[15−19] whereas dineolignans have been found in Magnoliaceae and Saururaceae.[20] In Magnoliaceae, which is known to be a rich source of lignans of manifold structures as well as compounds of mixed biosynthetic origin such as monoterpenyl or sesquiterpenyl lignans, dineolignans have been reported from *Magnolia officinalis* Rehder & Wilson and *M. obovata* Thunb. (= *M. hypoleuca* Sieb. & Zucc.).[21,22] A trineolignan, i.e., magnolianin, has been reported only from the bark of *M. obovata*.[23] The occurrence of dineolignans bearing additional 4-allylphenyl moieties as described herein for garrettilignans A and B has not been reported previously.

Experimental Section

General Experimental Procedures. Optical rotations were measured in MeOH on a Perkin-Elmer 341 polarimeter. UV−vis spectra were recorded on a UV-160A spectrophotometer (Shimadzu). IR spectra were taken as KBr pellets on a Perkin-Elmer 281 spectrophotometer. All 1D (^{1}H and ^{13}C) and 2D (COSY, HMBC, and HSQC) NMR spectra were recorded at 298 K on a Varian Unity Inova 600 MHz spectrometer using $CDCl_3$ as solvent and referenced to TMS as internal standard. EIMS were recorded on a Hewlett-Packard HP 6890 instrument fitted with a HP 7890 detector. ESIMS for compounds **1**, **2**, and **6** were measured in positive and negative mode on a Thermo Finnigan LQ Deca XP^{PLUS} mass spectrometer with autosampler using a SB-C18 Zorbax column (3.5 μm; 150 × 2.1 mm; Agilent Technologies) with a guard column at a flow rate of 300 μL/min using an acetonitrile gradient in water. ESI-MS spectra for compound **1a** were recorded on a MALDI Synapt HDMS System (Waters, Milford, MA) in positive ion V time-of-flight mode using a LockSpray dual electrospray ion source. Leu-enkephalin was used for lock-mass correction.

High-Resolution LC-MS Analysis. High-resolution mass spectra were obtained using an Agilent 1100 HPLC coupled to a JEOL AccuTOF (JMS-T100LC) (Peabody, MA). All isolated compounds were prepared in MeOH and injected directly into a 0.3 mL/min stream of either MeOH or 80% MeOH/20% deionized H_2O. A 20 μL sample (approximately 0.1 mg/mL) was injected manually at 0.5 min, while mass drift compensation standards [L-tryptophan (negative ion), PEG (positive ion)] were injected at 1.5 min over the course of a 2 min run.

Semipreparative and analytical HPLC separations were performed using an Agilent 1100 Series instrument equipped with a diode-array detector. Compound mixtures were separated on an HPLC preparative column packed with LiChrosorb RP-18 (7 μm, 250 × 10 mm, Merck, Darmstadt). Analytical HPLC-DAD analysis was performed using a SB-C18 Zorbax column (3.5 μm; 150 × 2.1 mm; Agilent Technologies) equipped with a guard column at a flow rate of 300 μL/min and a gradient elution program. Preparative HPLC was performed on a Varian R PrepStar SD-1 with a Dynamax R solvent delivery system and UV detector. For TLC analysis, precoated Si60 F_{254} plates (Merck) were used. Detection was performed under UV light at 254 and 366 nm, and visualization with spraying with vanillin−sulfuric acid reagent and heating.

Acetylation of **1** or **2**, respectively, was achieved by dissolving 20 mg of each of the compounds in 1 mL of absolute pyridine and adding 200 μL of acetic anhydride. The mixture was stirred at room temperature overnight, poured into 8 mL of H_2O, and then extracted with 2 mL of CH_2Cl_2 (3×). The combined and dried CH_2Cl_2 layers were evaporated to yield ca. 17 and 20 mg of crude **1a** and **2a**, respectively. The crude compounds were then purified by semipreparative HPLC using CH_3CN (90 → 100% in H_2O) to yield 7 and 8 mg of **1a** and **2a**, respectively.

Plant Material. Leaves of *Magnolia garrettii* Craib were collected in August 2009 from a specimen growing in the temperate house of the Botanical Garden in Graz. A voucher specimen is deposited at the Herbarium of the Institute of Plant Sciences at the University of Graz.

Extraction and Isolation. The dried and powdered leaves (1280 g) of *M. garrettii* were extracted with CH_2Cl_2 by percolation to yield a residue of 34 g. About 40 g of silica gel (40−63 μm) was coated with a portion (20 g) of the crude CH_2Cl_2 extract for fractionation (VLC) using a gradient of *n*-hexane/EtOAc from 100% *n*-hexane within six gradient steps of 5−10−15−20−50% → 100% EtOAc each using 500 mL of eluent, resulting in 15 fractions, V1−V15. Fractions V4−V14

Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1**, **1a**, **2**, and **2a** (600 and 150 MHz, in $CDCl_3$ at 25 °C)

	1		**1a**		**2**		**2a**	
	δ_H mult. (*J*, Hz)	δ_C	δ_H mult. (*J*, Hz)	δ_C	δ_H mult. (*J*, Hz)	δ_C	δ_H mult. (*J*, Hz)	δ_C
				Subunit A				
1		155.7 s		155.7 s		155.8 s		155.4 s
2/6	6.98 d (8.4)	118.1 d	6.84 d (8.4)	118.0 d	6.85 m	117.2 d	6.88 m	118.3 d
3/5	7.13 d (8.4)	129.7 d	7.08 d (8.4)	129.5 d	7.08 m	129.5 d	7.09 m	129.6 d
4		134.7 s		134.3 s		134.2 s		134.9 s
7	3.36 m	39.4 t	3.35 m	39.5 t	3.33 m	39.4 t	3.34 m	39.4 t
	3.36 m		3.35 m		3.33 m		3.34 m	
8	5.95 m	137.6 d	5.93 m	137.6 d	5.93 m	137.5 d	5.93 m	137.5 d
9	5.06 m	115.6 t	5.05 m	115.6 t	5.05 m	115.6 t	5.05 m	115.6 t
	5.06 m		5.05 m		5.05 m		5.05 m	
				Subunit B				
1		154.5 s		154.5 s		154.3 s		154.5 s
2/6	6.85 d (8.4)	118.0 d	6.88 d (8.4)	118.8 d	6.84 m	118.1 d	6.85 m	118.7 d
3/5	7.09 d (8.4)	130.0 d	7.07 d (8.4)	129.9 d	7.05 d (8.4)	129.9 d	7.09 m	129.9 d
4		135.6 s		135.6 s		135.7 s		137.7 s
7	3.34 m	39.5 t	3.33 m	39.5 t	3.32 m	39.4 t	3.34 m	39.4 t
	3.34 m		3.33 m		3.32 m		3.34 m	
8	5.93 m	137.2 d	5.93 m	137.3 d	5.93 m	137.2 d	5.93 m	137.3 d
9	5.06 m	116.0 t	5.05 m	115.9 t	5.05 m	115.9 t	5.05 m	116.0 t
	5.06 m		5.05 m		5.05 m		5.05 m	
				Subunit C				
1		155.6 s		155.2 s		155.7 s		155.9 s
2/6	6.75 d (8.4)	117.5 d	6.75 d (8.4)	117.8 d	6.87 m	117.6 d	6.88 m	117.8 d
3/5	7.07 d (8.4)	129.6 d	7.01 d (8.4)	129.7 d	7.05 m	129.5 d	7.09 m	129.5 d
4		134.5 s		134.6 s		134.4 s		134.9 s
7	3.32 m	39.4 t	3.30 m	39.5 t	3.30 m	39.4 t	3.34 m	39.4 t
	3.32 m		3.30 m		3.30 m		3.34 m	
8	5.93 m	137.6 d	5.93 m	137.5 d	5.93 m	137.5 d	5.93 m	137.5 d
9	5.06 m	115.7 t	5.05 m	115.7 t	5.06 m	115.6 t	5.05 m	116.6 t
	5.06 m		5.05 m		5.06 m		5.05 m	
				Subunit D				
1		135.2 s		140.1 s		136.5 s		130.8 s
2		149.1 s		149.6 s		143.4 s		149.5 s
3	6.22 s	111.6 d	6.58 s	118.6 d	6.43 s	114.4 d	6.42 s	113.2 d
4		133.3 s		136.1 s		131.3 s		136.5 s
5	6.55 s	111.8 d	6.63 s	118.1 d	6.35 s	110.0 s	6.48 s	109.7 d
6		150.6 s		144.2 s		146.5 s		151.2 s
7	3.18 m	39.8 t	3.23 m	39.4 t	3.15 m	39.6 t	3.19 m	40.0 t
	3.18 m		3.23 m		3.15 m		3.19 m	
8	5.84 m	136.9 d	5.83 m	136.4 d	5.82 m	137.1 d	5.93 m	138.8 d
9	5.00 m	116.0 t	5.00 m	116.5 t	4.99 m	115.9 t	5.00 m	116.4 t
	5.04 m		5.00 m		4.99 m		5.04 m	
				Subunit E				
1		135.5 s		134.1 s		135.3 s		134.3 s
2′		145.2 s		150.4 s		144.4 s		150.6 s
3′	6.66 s	110.0 d	6.85 s	115.9 d	6.79 s	109.8 d	6.98 s	115.8 d
4		127.7 s		135.2 s		128.0 s		n.d.
5	6.42 s	109.4 d	6.98 s	116.8 d	6.51 s	109.5 d	7.06 s	116.8 d
6		144.2 s		143.9 s		145.4 s		144.1 s
7	4.76 m	75.9 d	5.00 m	74.2 d	4.90 m	76.1 d	5.13 m	74.7 d
8	4.06 m	76.2 d	4.07 m	76.0 d	4.19 m	76.1 d	4.15 m	76.1 d
9	3.93 m	71.9 t	4.09 m	70.9 t	4.08 m	68.6 t	4.24 m	67.7 t
	3.93 m		4.09 m		3.95 m		3.94 m	
				Subunit F				
1		132.5 s		133.3 s		133.2 s		133.5 s
2		145.3 s		145.2 s		144.9 s		145.1 s
3	6.39 s	112.5 d	6.34 s	118.8 d	6.39 s	113.0 d	6.39 s	113.3 d
4		133.3 s		132.7 s		133.2 s		133.0 s
5	6.54 s	112.0 d	6.50	112.1 d	6.57 s	112.3 d	6.57 s	112.3 d
6		144.5 s		143.9 s		144.6 s		144.1 s
7	3.19 m	39.6 t	3.19 m	39.5 t	3.19 m	39.5 t	3.21 m	39.5 t
	3.19 m		3.19 m		3.19 m		3.21 m	
8	5.84 m	136.9 d	5.85 m	137.0 d	5.84 m	136.9 d	5.86 m	136.9 d
9	5.00 m	116.0 t	5.00 m	115.8 t	4.98 m	115.9 t	5.01 m	116.0 t
	5.04 m		5.04 m		4.98 m		5.01 m	
				Acetates				
1				169.2 s				168.4 s
2			2.19 s	20.5 q			2.05 s	20.1 q
1′				167.8 s				167.9 s
2′			2.25 s	20.6 q			2.28 s	20.6 q
1″				167.2 s				167.4 s
2″			2.19 s	20.2 q			2.19 s	20.2 q

were evaluated on the basis of their TLC patterns as well as by analytical HPLC together with ESI-LC-MS analysis. A portion of fraction V6 (100 mg) was purified by solid-phase extraction (SPE) on cartridges (5 g of RP-18, 10 μm, Sorbent Technologies) using a stepwise gradient of MeOH/water, 60:40 → 100:0. Preparative HPLC using CH_3CN (68% in H_2O) of the major fraction yielded 2 mg of methylhonokiol (**5**) and 19 mg of obovatol (**6**). Similarly, a portion (200 mg) of V9 was purified in the same manner to yield 2 mg of magnolol (**3**), 5 mg of honokiol (**4**), and 7 mg of obovatol (**6**). On the basis of ESI-LC-MS analysis, V10 (450 mg) turned out to be the most interesting fraction. A portion of V10 (200 mg) was subjected to SPE (5 g of RP-18, 10 μm, Sorbent Technologies) using a stepwise gradient of MeOH/water (75:40 → 100:0) and yielded 120 mg of a mixture of **1** and **2**. This mixture was then separated by preparative HPLC using CH_3CN (76% in H_2O) to yield **1** (43 mg) and **2** (51 mg).

Garrettilignan A (1): slightly brown solid; $[\alpha]_D^{21}$ +6.4 (*c* 2.84, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 207 (5.0), 274 (4.2) nm; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 843.01 $[M - H_2O + H]^+$ (100); negative ESIMS *m/z* 841.1 $[M - H_2O - H]^-$ (100); HRESIMS *m/z* 865.3418 $[M - H_2O + Na]^+$ (calcd for $C_{54}H_{50}O_9Na$, 865.3353).

Garrettilignan B (2): dark brown solid; $[\alpha]_D^{21}$ +1.4 (*c* 10.9, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 207 (5.1), 275 (4.4) nm; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 843.01 $[M - H_2O + H]^+$ (100); negative ESIMS *m/z* 841.1 $[M - H_2O - H]^-$ (100); HRESIMS *m/z* 865.3418 $[M - H_2O + Na]^+$ (calcd for $C_{54}H_{50}O_9Na$, 865.3353).

Acetylated garrettilignan A (1a): yellow oil; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 991.4 $[M - H_2O + Na]^+$ (100).

Acetylated garrettilignan B (2a): yellow oil; ^1H and ^{13}C NMR data, see Table 1.

Magnolol (3): clear crystals; ^1H and ^{13}C NMR ($CDCl_3$) in agreement with literature data;[23] GC-EIMS *m/z* 266 (100).

Honokiol (4): white solid; ^1H and ^{13}C NMR ($CDCl_3$) in agreement with literature data;[23] GC-EIMS *m/z* 266 (100).

4′-Methylhonokiol (5): clear oil; ^1H and ^{13}C NMR ($CDCl_3$) in agreement with literature data;[23] GC-EIMS *m/z* 280 (100), 251 (22).

Obovatol (6): white solid; ^1H and ^{13}C NMR ($CDCl_3$) in agreement with literature data;[24] positive ESIMS *m/z* 283.21 $[M + H]^+$ (100) (calcd for $C_{18}H_{19}O_3$, 283.131).

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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