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Benzodihydrofurans from *Cyperus teneriffae*

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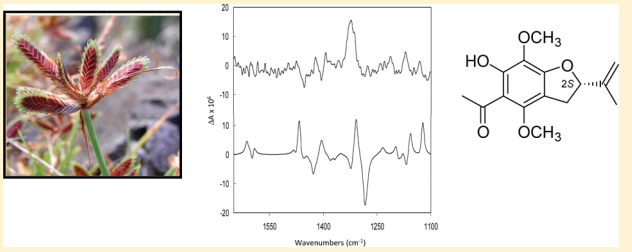
Supporting Information

ABSTRACT: Three new benzodihydrofurans (**1**−**3**) and seven known aromatic compounds (**4**−**10**) were isolated from the roots of *Cyperus teneriffae*. Vibrational circular dichroism spectroscopy was used to define the absolute configuration of **1**.



Cyperaceae is a family of monocotyledonous flowering plants known as sedges, which superficially resemble grasses or rushes. The family comprises some 4000 species described in about 70 genera. These species are widely distributed, with the centers of diversity for the group occurring in tropical Asia and tropical South America. While sedges may be found growing in all types of soils, many are associated with wetlands or with poor soils. The genus *Cyperus* includes about 600 species, some of which are used in folk medicine. Rhizomes of *Cyperus rotundus* L., for example, have been used in traditional Chinese medicine as estrogenic and anti-inflammatory agents for the treatment of menstrual disorders, stomachache, and bowel disorders.[1] The extract of *C. rotundus* L. rhizomes has shown antidiabetic,[2] acetylcholinesterase inhibitory,[3] and antidiarrheal activity.[4] It has also been shown to inhibit nitric oxide and superoxide production.[5] *C. conglomeratus* has been used in expectorant, emollient, diuretic, stimulant, analgesic, and antihelmintic treatments.[6] The whole plant of *C. longus* has been used as a diuretic and tonic in Egyptian traditional medicine.[7] Previous chemical studies carried out on *Cyperus* species have led to the isolation of coumarins,[8] quinones,[9] benzofurans,[10] aurones,[11] sesquiterpenes,[12] and flavanoids.[13]

C. teneriffae, a species endemic to the Canary Islands, is mainly distributed in Gran Canaria (Moya and Cuesta de Silva) and Tenerife (Masca, Suculum, and Güimar).[14] Given that metabolites present in *Cyperus* species possess interesting bioactivities and the absence of any previous phytochemical studies on *C. teneriffae*, we examined this species. In this paper we describe the isolation and structural elucidation of three new benzofurans (**1**−**3**) and seven known aromatic compounds (**4**−**10**). Vibrational circular dichroism (VCD) spectroscopy was used to determine the absolute configuration of **1**.

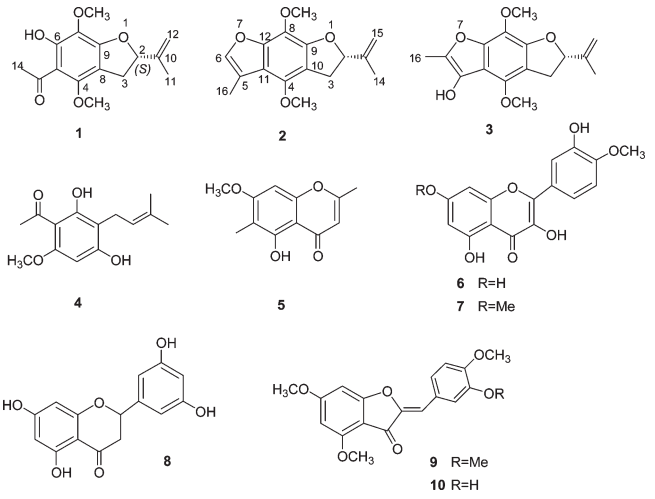


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Table 1. ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) Data of Compounds 1−3

	1		2		3	
position	δ_H, J (Hz)	δ_C	δ_H, J (Hz)	δ_C	δ_H, J (Hz)	δ_C
2	5.29 dd (9.5, 7.5)	87.7 CH	5.25 dd (9.3, 8.0)	87.1 CH	5.34 dd (9.3, 8.0)	87.9 CH
3	3.46 dd (15.0, 9.5) 3.10 dd (15.0, 7.5)	32.9 CH_2	3.47 dd (15.1, 9.3) 3.15 dd (15.1, 8.0)	32.7 CH_2	3.58 dd (15.3, 9.3) 3.25 dd (15.4, 8.0)	33.0 CH_2
4		154.0 C		144.3 C		147.3 C
5		108.9 C		116.1 C		149.2 C
6		159.3 C	7.19 d (1.3)	139.7 CH		122.5 C
7		128.0 C				
8		158.3 C		125.8 C		125.3 C
9		107.9 C		147.9 C		153.7 C
10		142.8 C		113.1 C		114.7 C
11	1.78 s	16.9 C		115.2 C		115.4 C
12	5.11 s 4.96 s	113.1 CH_2		148.3 C		144.6 C
13		203.3 C		143.5 C		142.8 C
14	2.63 s	32.0 CH_3	1.79 s	16.9 CH_3	1.82 s	17.0 CH_3
15			5.10 s 4.91 s	112.2CH_2	5.15 s 5.00 s	113.1 CH_2
16			2.28 d (1.3)	9.2 CH_3	2.81 s	11.3 CH_3
OMe	3.89 s	59.3 CH_3	4.06 s	60.5 CH_3	4.11 s	60.9 CH_3
OMe	3.89 s	60.6 CH_3	3.86 s	60.4 CH_3	3.98 s	59.9 CH_3
OH	13.94 s					

RESULTS AND DISCUSSION

Repeated chromatography of an EtOH extract of the roots of *C. teneriffae* over silica gel and Sephadex LH-20 yielded three new benzofurans (**1**−**3**) and seven known aromatic compounds (**4**−**10**). The known compounds were identified by comparison with published spectroscopic and other physical data as preremirol (**4**),[15] eugenetin (**5**),[16] tamarixetin (**6**),[17] ombuin (**7**),[18] 5,7,3′,5′-tetrahydroxyflavanone (**8**),[19] 4,6,3′,4′-tetramethoxyaurone (**9**),[20] and 3′-hydroxy-4,6,4′-trimethoxyaurone (**10**).[21] The semisynthetic compound **10** obtained from methylation of auresin followed by removal of the sugar residue[21] is reported here for the first time as a natural product.

Compound **1** was isolated as an amber viscous oil with a positive specific rotation ($[\alpha]^{20}_D$ +6.8, *c* 0.3, $CHCl_3$) and molecular formula $C_{15}H_{18}O_5$ as determined by HREIMS and ^{13}C NMR-DEPT experiments. The ^{1}H NMR spectrum of **1** (Table 1) displayed a methyl singlet at δ 2.63 attributable to a methyl ketone, two methoxy groups at δ 3.89 (6H), and a signal due to a hydrogen-bonded hydroxy proton at δ 13.94. The ^{1}H NMR spectrum also showed signals characteristic of a 2-substituted-2,3-dihydrobenzofuran moiety:[22] three double doublets at δ 5.29 (J = 9.5, 7.5 Hz, H-2), 3.46 (J = 15.0, 9.5 Hz, H-3a), and 3.10 (J = 15.0, 7.5 Hz, H-3b). The presence of an isopropenyl group was also evident [δ 1.78 (3H, s), 4.96 (1H, s), and 5.11 (1H, s)]. Its ^{13}C NMR and DEPT spectra showed the presence of a carbonyl carbon at δ 203.3, six quaternary aromatic carbons at δ 107.9, 108.9, 128.0, 154.0, 158.3, and 159.3, and one oxymethine carbon at δ 87.7. These data indicate that **1** is a 2,3-dihydrobenzofuran possessing two methoxy groups, a hydroxy group, a methyl ketone moiety, and an isopropenyl group. The locations of these groups were established by the ^{1}H−^{13}C long-range correlations in the HMBC spectrum and by the NOEs in the ROESY spectrum (Figure 1).

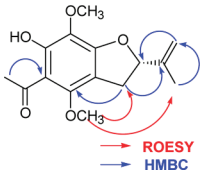

Figure 1. Selected HMBC and ROESY correlations for compound **1**.

Table 2. B3LYP-Calculated Relative Energies (kcal mol^{-1}) and Conformational Population (%) for the Most Stable Conformers of (2*S*)-1

conf	$\Delta E_{6\text{-}31G(d)}$[a]	%[b]	ΔE_{DGDZVP}[c]	%[d]
1a	0.00	21.1	0.00	20.8
1b	0.17	15.4	0.26	13.6
1c	0.18	15.3	0.26	13.6
1d	0.18	15.3	0.17	15.1
1e	0.37	11.2	0.29	12.9
1f	0.48	9.1	0.42	9.9
1g	0.66	6.6	0.59	7.6
1i	0.75	5.9	0.67	6.5

[a] Relative to **1a** with $E_{6\text{-}31G(d)}$ = −601469.88 kcal mol^{-1}. [b] Calculated using free energy values from the Spartan'08 program according to $\Delta G = -RT \ln K$. [c] Relative to **1a** with E_{DGDZVP} = −505677.31 kcal mol^{-1}. [d] Calculated using free energy values from Gaussian 03W according to $\Delta G = -RT \ln K$.

From the positive specific rotation displayed by **1** the 2*S* absolute configuration could be suggested in analogy with related molecules.[23] However, to unequivocally determine the absolute configuration, we analyzed this compound by vibrational circular dichroism. VCD analysis has been used in recent years for determining the absolute configuration of many natural products,[24] including sesquiterpenes, peptides, coumarins, and alkaloids.[25]

The theoretical VCD study of (2*S*)-**1** was started by employing molecular modeling, which involved the use of the Monte Carlo protocol[26] at the MMFF94 level.[27] Considering a cutoff of 10 kcal mol^{-1}, 20 minimum energy conformers were inferred.

All these structures were submitted to a single-point calculation using density functional theory[28] (DFT) at the B3LYP/6-31G(d) level. Exploring the first 5 kcal mol^{-1}, this optimization provides only eight conformers with ΔE = 0.75 kcal mol^{-1} (Table 2). The ninth conformer has ΔE = 5.96 kcal mol^{-1} with respect to the most stable one and contributes insignificantly to the conformational population. The eight conformers were reoptimized by DFT at the B3LYP/DGDZVP level, and the IR and VCD frequencies were calculated using the same functional and basis set. The use of this B3LYP/DGDZVP combination of basis set and functional has shown a superior balance between computer cost and VCD spectra accuracy,[29] a situation that seems to be associated with the fact that DGauss basis sets, such as DGDZVP, are optimized for DFT methods.[30,31] After B3LYP/DGDZVP optimization, the eight relevant conformers

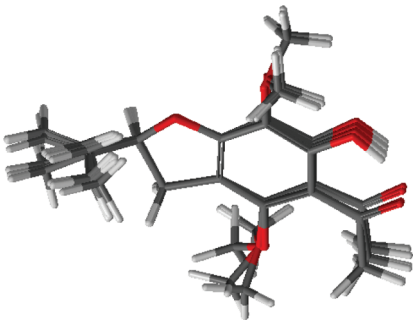

Figure 2. Superimposed conformers **1a**−**g**.

showed essentially the same conformation for the dihydrobenzofuran system, as evidenced by the superimposed molecular arrangement in Figure 2.

All conformers show a hydrogen-bonded hydroxy proton, and different orientations for the methoxy and the isopropylidene groups. The most stable conformer (**1a**) has $H_{2\alpha}-H_{3\alpha}$ and $H_{2\alpha}-H_{3\beta}$ dihedral angles of −23.5° and −142.6°, respectively, which when using a generalized Karplus-type equation[32] correspond to coupling constants of 7.1 and 9.1 Hz, respectively. Experimental coupling constants are $J_{2\alpha,3\alpha}$ = 7.5 and $J_{2\alpha,3\beta}$ = 9.5 Hz, thus validating the predominant conformations modeled by DFT calculations. The calculated VCD spectra of these eight conformers of **1** were combined into a single weighted plot according to the Boltzmann conformational population derived from their relative free energy values. The spectrum thus calculated shows good agreement with the experimental VCD spectrum (Figure 3), revealing the 2*S* absolute configuration. Such a configuration is in agreement with the positive specific rotation reported for several natural dihydrofurocromones isolated from *Prionosciadium thapsoides*.[23] Thus, compound **1** is 1-(2,3-dihydro-6-hydroxy-4,7-dimethoxy-2*S*-(prop-1-en-2-yl)benzofuran-5-yl)ethanone.

Compound **2** was isolated as a viscous oil with the molecular formula $C_{16}H_{18}O_4$. Its spectroscopic data revealed a structure similar to compound **1**. The ^{1}H NMR spectrum exhibited signals characteristic of a 2-isopropenyldihydrobenzofuran moiety [δ 5.25 (dd, J = 9.3, 8.0 Hz, H-2), 3.47 (dd, J = 15.1, 9.3 Hz, H-3a), 3.15 (dd, J = 15.1, 8.0 Hz, H-3b), 5.10 (s, H-15a), 4.91 (s, H-15b), and 1.79 (s, H-14)]. The ^{1}H NMR spectrum also displayed two methyl singlets at δ 4.06 and 3.86 corresponding to two methoxy groups, a doublet at δ 7.19 (1H, J = 1.3 Hz) assignable to an aromatic hydrogen, and a methyl doublet at δ 2.28 (J = 1.3 Hz). These signals, together with the existence of a methine carbon at δ 139.7 and a quaternary carbon at δ 116.1 in the ^{13}C NMR and DEPT spectra, suggest the presence in **2** of an additional furan ring. The existence of this ring agrees with the fact that **2** has eight degrees of unsaturation. The structure of **2** was validated from the following HMBC correlations: H-2/C-3, H-3/C-2, H-3/C-13, H-6/C-11, H-6/C-12, H-6/C-16, H-14/C-2, H-14/C-15, H-14/C-13, H-15/C-2, H-15/C-14, OCH_3/C-4, and OCH_3/C-8.

Compound **2** has a tetrasubstituted 1,4-dimethoxyphenyl B ring instead of a 1,4-benzoquinone moiety in the known compound cyperaquinone.[22] The absolute configuration at C-2 was assumed to be 2*S* by biogenetic considerations.[33] All these data permitted establishment of the structure of compound **2** as 2*S*-isopropenyl-4,8-dimethoxy-5-methyl-2,3-dihydrobenzo[1,2-*b*;5,4-*b*′]difuran.

Compound **3** was isolated as a yellow oil with the molecular formula $C_{16}H_{18}O_5$, assigned by HREIMS. Its IR spectrum showed

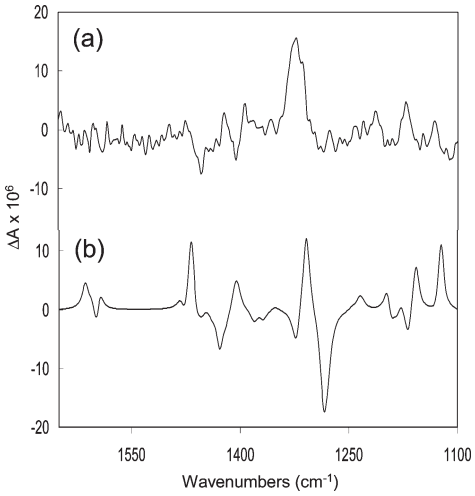

Figure 3. DFT/B3LYP/DGDZVP-calculated (a) and experimental (b) VCD spectra for (2*S*)-**1**.

an absorption band for hydroxy groups (3442 cm^{-1}). The ^{1}H NMR data were similar to those of **2**. The main differences were the absence of the aromatic hydrogen at δ 7.19 and the downfield shielding of the methyl group on the furan ring. Its ^{13}C NMR spectrum showed the presence of eight quaternary aromatic carbons at δ 114.7, 115.4, 122.5, 125.3, 144.6, 147.3, 149.2, and 153.7 and the presence of an isopropenyl group (δ 113.1 (t), 142.8 (s), 17.0 (q)). These data suggest that compound **3** has a furan and a dihydrofuran ring fused to a central 1,4-dimethoxybenzene moiety, with a hydroxy and a methyl group on the furan ring. The key HMBC correlations between the methyl group at δ 2.81 and the quaternary carbons at δ 115.4, 122.5, and 149.2 established the substitution of the furan ring as depicted. This information together with the NOEs obtained in the GOESY experiment (see Supporting Information) determined the structure of compound **3** as 2*S*-isopropenyl-4,8-dimethoxy-5-hydroxy-6-methyl-2,3-dihydrobenzo[1,2-*b*;5,4-*b*′]difuran.

Biogenetically, compound **1** could be derived from the prenylation of phloroacetophenone, followed by epoxidation and intramolecular opening of the corresponding epoxide. Compounds **2** and **3** may be biosynthesized in a similar way from phloroglucinol (see the Supporting Information).[33] Compounds having a furan or dihydrofuran ring fused to a 1,4-dimethoxyphenyl moiety are rare natural products. Only bibenzyl derivatives from *Radula* species[34] and a few benzodihydrofurans from *Lonchocarpus laxiflorus* have been reported.[35]

Since metabolites isolated from *Cyperus* showed estrogenic activity,[1,9c,36] the isolated metabolites **1**, **2**, **4**, **6**, and **8**−**10** were subjected to evaluation of their potential as antiestrogenic agents. We employ the E-Screen proliferation assay, which uses the human breast cancer cell line MCF-7 BUS, to assess the proliferation ability of any given drug.[37] However, none of them showed significant activity.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. UV spectra were recorded in absolute EtOH on a JASCO V-560 spectrophotometer. IR spectra were obtained using a Bruker IFS28/55 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz

respectively, with TMS as the internal reference. 2D NMR experiments were conducted on a Bruker WP-500 SY NMR spectrometer at 500 MHz. High- and low-resolution mass spectra were obtained on a VG Autospec spectrometer. Macherey-Nagel polygram Sil G/UV254 and Analtech silica gel GF preparative layer with UV254 were used for TLC. Silica gel (0.2−0.63 mm) was used for column chromatography. Silica gel 60 (Merck) was used on a Harrison Research 7924T Chromatotron.

IR and VCD Measurements. The IR spectra were obtained using a BioTools-BOMEM Chiral*IR* FT-VCD spectrophotometer equipped with dual photoelastic modulation. A sample of 4.5 mg of **1** was dissolved in 150 μL of 100% atom-D $CDCl_3$ and placed in a BaF_2 cell with a path length of 150 μm, acquiring data at a resolution of 4 cm^{-1}. This procedure was repeated four times. The identity of **1** was verified by ^1H NMR measurement immediately prior and after VCD measurements.

DFT Calculations. The conformational search was started using a Monte Carlo guided protocol considering an initial energy cutoff of 10 $kcalmol^{-1}$ above the global minimum value. All structures were submitted to a single-point energy calculation at the B3LYP/6-31G(d) level. The eight relevant conformers, found in a 5 kcal mol^{-1} energy range, were further optimized using the B3LYP hybrid functional and the DGDZVP basis set, and then IR and VCD frequencies were calculated at the same level of theory. Frequencies were scaled using an anharmonicity factor of 0.97 and plotted as Lorentzian bands with half-widths of 6 cm^{-1}. The final computed VCD spectrum of **1** was generated by weighting the individual VCD spectra according to the free energy values. Monte Carlo search and single-point energy calculations were made using the Spartan'08 software package (Wavefunction, Irvine, CA, USA), while geometry reoptimizations and vibrational spectra were calculated using the Gaussian 03W software package (Gaussian, Inc., Wallingford, CT, USA). Typically, for optimization around 6 h, an additional 13 h for IR and VCD calculations of computational time were required per conformer when using a desktop personal computer with 4 GB of RAM operated at 3 GHz.

Plant Material. Specimens of *Cyperus teneriffae* Poir were collected in the northeast of Tenerife (Suculum de San Andrés). Plant material was identified by the botanist Dr. M. Del Arco. A voucher specimen is on file (TFC 43373) at the Herbarium of Botánica of the Departamento de Biología Vegetal, Universidad de La Laguna.

Extraction and Isolation. Dried roots of *C. teneriffae* (3.2 kg) were extracted with EtOH in a Soxhlet apparatus. Evaporation of the solvent under reduced pressure provided 93 g of a dark extract. This residue was chromatographed on silica gel eluted with mixtures of *n*-hexane/EtOAc of increasing polarity. Eight fractions, A−H, were separated and further chromatographed on Sephadex LH-20 and Si gel using as solvents mixtures of *n*-hexane/$CHCl_3$/MeOH (2:1:1) and *n*-hexane/EtOAc, respectively. Some of the eluted products were separated by preparative TLC. Compound **2** (400 mg) was isolated from fraction B. Fraction D yielded **1** (20 mg), **3** (5 mg), and eugenetin (**5**).[16] Preremirol (**4**)[15] was isolated from fraction F and 4,6,3′,4′-tetramethoxyaurone (**9**)[20] (20 mg) from fraction H. Fraction I afforded 5,7, 3′,5′-tetrahydroxyflavanone (**8**)[19] (40 mg) and ombuin (**7**)[18] (10 mg). Tamarixetin (**6**)[17] (30 mg), 3′-hydroxy-4,6,4′-trimethoxyaurone (**10**)[21] (30 mg), and 4,6,3′,4′-tetramethoxyaurone (**9**)[20] (40 mg) were isolated from fraction H.

1-[2,3-Dihydro-6-hydroxy-4,7-dimethoxy-2*S*-(prop-1-en-2-yl)benzofuran-5-yl]ethanone (1): amber oil; $[\alpha]^{20}_D$ +6.8 (*c* 0.3, $CHCl_3$); IR (film) γ_{max} 3082, 2936, 2895, 1616, 1442, 1421, 1366, 1332, 1289, 1269, 1202, 1174, 1132, 1087, 1062, 978, 902, 858, 773, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 1); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 278 $[M]^{+\cdot}$ (100), 263 (97), 245 (11), 233 (9), 231 (7), 230 (2), 221 (2), 220 (4); HREIMS 278.1158 (calcd for $C_{15}H_{18}O_5$ 278.1188).

2*S*-Isopropenyl-4,8-dimethoxy-5-methyl-2,3-dihydrobenzo-[1,2-*b*;5,4-*b*′]difuran (2): amber oil; $[\alpha]^{20}_D$ +13.6 (*c* 0.5, $CHCl_3$); IR (film) γ_{max} 3080, 2930, 2855, 2042, 1809, 1726, 1648, 1507, 1436, 1335, 1290, 1225,1138, 1102, 1037, 987, 907, 800, 738, 615, 578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 1); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 274 $[M]^{+\cdot}$ (100), 259 (49), 248 (16), 244 (16), 233 (21), 229 (13), 228 (14), 227 (20), 211 (44); HREIMS 274.1212 (calcd for $C_{16}H_{18}O_4$ 274.1191).

2*S*-Isopropenyl-4,8-dimethoxy-5-hydroxy-6-methyl-2,3-dihydrobenzo[1,2-*b*;5,4-*b*′]difuran (3): amber oil; $[\alpha]^{20}_D$ +0.71 (*c* 1.8, $CHCl_3$); IR (film) γ_{max} 3442, 2923, 2852, 1713, 1609, 1573, 1492, 1438, 1362, 1331, 1307, 1283, 1245, 992, 899, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see Table 1); ^{13}C NMR (100 MHz, $CDCl_3$) (see Table 1); EIMS *m/z* 290 $[M]^{+\cdot}$ (10), 288 (100), 273 (78), 225 (20), 183 (10); HREIMS 290.1146 (calcd for $C_{16}H_{18}O_5$ 290.1154).

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra of the new compounds and schemes showing the possible biogenetic relationships between the isolated dihydrobenzofurans. This material is available free of charge via the Internet at http://pubs.acs.org.

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