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IRIDOIDS AND IRIDOID GLUCOSIDES FROM FRUITS OF *CRESCENTIA* CUJETE

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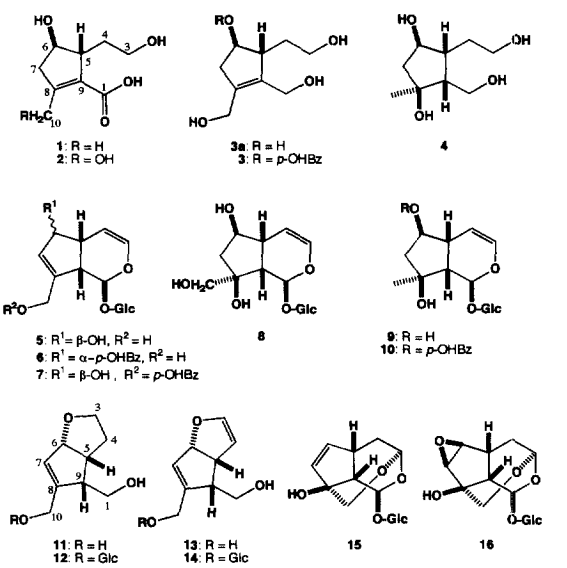
Key Word Index—*Crescentia cujete*; Bignoniaceae; fruits; iridoids; iridoid glycosides; crescentins I–V; crescentosides A, B and C.

Abstract—Further study on the constituents of the fruits of *Crescentia cujete* afforded 16 iridoids and iridoid glucosides. The structures of eight new compounds, named crescentins I–V and crescentosides A, B and C, were determined by analysis of their spectral data. Another eight known compounds were identified as ajugol, 6-*O*-*p*-hydroxybenzoylajugol, aucubin, 6-*O*-*p*-hydroxybenzoyl-6-epiaucubin, agnuside, ningpogenin, 5,7-bisdeoxycynanchoside and a degradation product of glutinoside. © 1997 Elsevier Science Ltd

INTRODUCTION

Crescentia cujete L. is widely distributed in South Asian countries. Naphtoquinones [1] and iridoid glycosides, aucubin, plumieride and asperuloside [2], have already been reported as the constituents of the leaves of this plant. The fruits of this plant have been used as a Vietnamese folk medicine, as an expectorant, antitussive, laxative and for stomach disorders. We have already isolated eight *n*-alkyl glycosides, three aromatic conjugated glucoses and a lignan glycoside from the fruits [3].

Further study on the constituents of the fruits afforded five new iridoids, named crescentins I (**1**), II (**2**), III (**3**), IV (**4**) and V (**13**), and three new iridoid glucosides, named crescentosides A (**12**), B (**14**) and C (**15**), together with eight known iridoids and iridoid glucosides (**5–11** and **16**). This paper deals with the identification and structural elucidation of these compounds.



RESULTS AND DISCUSSIONS

Chromatographic separation of the methanolic extract of the fruits of *C. cujete* afforded 16 compounds (**1–16**) as described in the Experimental section. Of these, seven compounds **5–11** were identified as aucubin (**5**) [4], 6-*O*-*p*-hydroxybenzoyl-6-epiaucubin (**6**) [5], agnuside (**7**) [6], 5,7-bisdeoxycynanchoside (**8**) [7], ajugol (**9**) [8], 6-*O*-*p*-hydroxybenzoylajugol (**10**) [9], ningpogenin (**11**) [10]. Compound **16** was identical to an artificial compound derived from glutinoside in the process of its structural determination [11], which has not been found in nature. The identification of these compounds was performed by analysis of their ^{1}H and ^{13}C NMR data, and mass spectra and subsequent comparison of these observed physical characteristics with previously published data.

The ^{13}C NMR spectral data revealed that crescentin I (**1**) is consistent with a tetra-substituted double bond (δ 133.7 and 141.3) and a carbonyl (δ 175.4), a methyl

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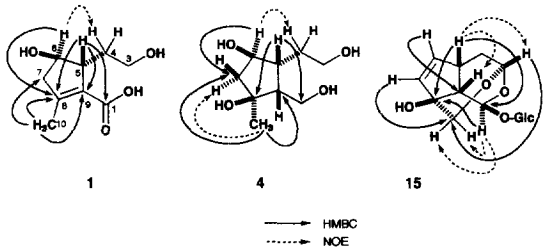

Fig 1.

(δ 14.5), two methylene (δ 33.2 and 45.4), a hydroxymethyl (δ 59.6), a methine (δ 52.2) and a hydroxymethylene (δ 74.5) groups. On methylation with diazomethane, compound **1** yielded a monomethyl ester which suggested the presence of a carboxyl group. The H-H COSY experiment showed the presence of a partial structure of C-3–C-7. Correlation of the remaining carbons, including the connectivity between the C-5 and C-9, and the C-7 and C-8, as well as the allocation of the carboxyl group, were corroborated by the HMBC measurement as shown in Fig. 1. With respect to the stereochemistry, the NOE measurement (Fig. 1) allowed the relative configuration assignments of C-5 and C-6, based on the observation of an NOE between the H-4a (δ 1.52) and H-6 (δ 3.91). However, the absolute configurations of these asymmetric carbons have not been determined. Based on the above results, the structure of crescentin I (**1**) was established as shown. The structures of the following compounds having the iridoid skeleton are also inscribed with tentative absolute configurations.

In the NMR spectra of crescentin II (**2**), the proton and carbon resonances corresponding to those of **1** were discernible, but lacked the methyl signal due to the C-10 (δ_C 14.5 and δ_H 1.69) of **1**, and instead had a hydroxymethyl signal (δ_C 60.9 and δ_H 4.07, 4.21). Furthermore, its quasi molecular ion peak at *m/z* 201 in the negative FAB-mass spectrum was 16 masses higher than that of **1**. Therefore, crescentin II (**2**) was assigned to be the C-10 hydroxylated congener of crescentin I (**1**).

The NMR data disclosed that crescentin III (**3**) is a phenolic conjugated iridoid with *p*-hydroxybenzoic acid. Further detailed analysis of the data showed that compound **3** is a modification of **1**, with CH_2OH (δ_C 58.4 and δ_H 4.57, 4.77) in place of the COOH on C-9. This part corresponds to eucommiol (**3a**) [12], but the absolute configurations of C-5 and C-6 are uncertain. The chemical shift of the H-6 (δ 5.92), and the observation of a H-C long-range correlation between the H-6 and the carbonyl carbon in the HMBC experiment of **3** permitted the allocation of the acyl moiety on C-6. Therefore, the structure of crescentin III (**3**) was formulated as 6-*O*-(*p*-hydroxybenzoyl)-eucommiol.

The ^1H and ^{13}C NMR spectra of crescentin IV (**4**) showed signals due to a methyl, two methylene, two methine, two hydroxymethyl and a hydroxymethine groups. In addition to these groups, the presence of a tertiary hydroxyl group was confirmed by measurement of the IR spectrum of its acetate obtained by acetylation with acetic anhydride–pyridine at room temperature. By the same analogy applied in the case of **1**, crescentin IV (**4**) was characterized from the results of detailed and concerted application of H-H COSY, HMBC and NOE experiments (Fig. 1).

The acid hydrolysis of crescentoside A (**12**) afforded D-glucose and an aglycone which was identified as compound **11** [10]. On comparison of the ^{13}NMR spectra of **11** and **12** the carbon signals due to C-8 and C-9 were shifted upfield (1.3 and 1.1 ppm) and C-10 was shifted downfield (8.2 ppm), while other signals remained almost unshifted. The glycosylation shifts suggested [13] that **12** is a glucoside of **11** with the linkage being at C-10. Accordingly, the structure of crescentoside A (**12**) was proposed to be ningpogenin-10-*O*-β-D-glucopyranoside.

The ^{13}C NMR spectrum of crescentin V (**13**) was very similar to that of **11** except for the signals due to a disubstituted double bond (δ 142.0 and 105.6). This double bond can only be assigned for C-3 and C-4 in the skeleton. Therefore, the structure of crescentin V (**13**) was defined as 3,4-dehydroningpogenin.

A comparison of the NMR spectral data of compound **13** with those of crescentoside B (**14**), as well as the result of the acid hydrolysis disclosed that **14** is a mono-β-D-glucopyranoside of **13**. The glycosylation shifts were observed for the carbon signals due to C-8 (−0.8 ppm), C-9 (−0.9 ppm) and C-10 (+8.4 ppm) of compound **14**. On the basis of these results, crescentoside B (**14**) was concluded to be 3,4-dehydroningpogenin-10-*O*-β-D-glucopyranoside.

Acid hydrolysis of crescentoside C (**15**) yielded D-glucose. Detailed analyses of the NMR data showed that **15** is an analogous compound of **16** [11], in which the epoxy group [δ_C 60.8 (C-6), 59.1 (C-7) and δ_H 3.46 (H-6), 3.55 (H-7)] was replaced by a disubstituted double bond [δ_C 138.2 (C-6), 132.1 (C-7) and δ_H 6.05 (C-6), 5.49 (C-7)]. In order to obtain more information regarding this presupposed structure, the HMBC and NOE experiments were performed and are illustrated in Fig. 1. These experiments agreed with the structure given.

As already mentioned in the introduction, aucubin, plumieride and asperuloside have been reported as the constituents of the leaves of *Crescentia cujete* [2]. The isolation of plumieride from Bignoniaceous plant is very interesting from the chemotaxonomical viewpoint, because this compound had been looked on as a characteristic constituent of Apocynaceous plants for a long time. Although we have isolated many iridoids and iridoid glucosides as discussed above, plumieride and asperuloside have not been obtained yet, from the fruits of this plant.

EXPERIMENTAL

General. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): TMS or dioxane as int. standard; CC: silica gel (Kieselgel 60, 70–230 mesh, Merck), styrene–divinyl-

benzene copolymer resin (Diaion HP-20, Mitsubishi Chem. Ind., Japan) MPLC: ODS-AQ 120-S50 (23 mm × 42 cm, YMC, Japan); HPLC; R-ODS-5 S-5 120A (25 mm × 25 cm, YMC, Japan). All solvent systems for chromatography were homogeneous unless otherwise stated. Acid hydrolysis of glycosides and identification of resulting monosaccharides: see ref. [14].

Plant material. Fruits of *Crescentia cujete* L. were collected in Long Thanh, Ba Ria-Vung Tau province, Vietnam in 1994. A voucher specimen has been deposited in the Herbarium of Ho Chi Minh City University of Medicine and Pharmacy.

Extraction and separation. Dried fruits (300 g) were extracted with hot MeOH. After removal of the solvent by evapn, the extract (162 g) was partitioned between H_2O and Et_2O. The H_2O layer was subjected to CC on styrene–divinylbenzene copolymer resin eluted with H_2O, 25% MeOH, 50% MeOH and MeOH, Successively. The 25% MeOH eluate was sepd into eight frs by CC on silica gel using EtOAc–EtOH–H_2O (8:2:1). Fr. 2 was purified by MPLC (12.5% MeOH) and HPLC (10% MeOH), successively, to afford **11** (240 mg) and **13** (10 mg). Fr. 3 was purified by HPLC (7% MeOH) to give **1** (29 mg), **2** (13 mg), **12** (18 mg), **14** (14 mg), **15** (35 mg) and **16** (20 mg). Fr. 4 was purified by HPLC (10% MeOH) to give **5** (61 mg), **8** (29 mg) and **9** (27 mg). The 50% MeOH eluate (1.2 g) was chromatographed on silica gel with EtOAc–EtOH–H_2O (40:5:1–8:2:1) to give seven frs. Fr. 2 was purified by MPLC (27% MeOH), and then HPLC (30% MeOH) to afford **3** (20 mg). Fr. 3 was purified by HPLC (37% MeOH) to give **6** (61 mg), **7** (10 mg) and **10** (22 mg). The H_2O eluate was extracted with *n*-BuOH satd with H_2O. The BuOH extract (1.1 g) was sepd into five frs by CC on silica gel using EtOAc–EtOH–H_2O (8:2:1). Fr. 4 was purified by MPLC (8% MeOH) and then HPLC (10% MeOH) to afford **4** (12 mg).

Crescentin I (**1**). Powder; $[\alpha]_D^{25}$ −43° (MeOH; *c* 1.0). FAB-MS (negative): *m/z* 185.0803 $[M-H]^-$ ($C_9H_{13}O_4$ requires; 185.0814). ^1H NMR (D_2O): δ 3.91 (1H, *dd*, *J* = 4.6, 2.6 Hz, H-6), 3.45 (2H, *t*, *J* = 6.8 Hz, H-3), 2.67 (1H, *dd*, *J* = 18.1, 4.6 Hz, H-7a), 2.64 (1H, *m*, H-5), 2.04 (1H, *d*, *J* = 18.1 Hz, H-7b), 1.69 (3H, *s*, H-10), 1.52 (1H, *dt*, *J* = 13.9, 6.8 Hz, H-4a), 1.39 (1H, *dt*, *J* = 13.9, 6.8 Hz, H-4b). ^{13}C NMR: Table 1.

Crescentin II (**2**). Powder; $[\alpha]_D^{25}$ −21° (MeOH; *c* 1.0). FAB-MS (negative): *m/z* 201.0753 $[M-H]^-$ ($C_9H_{13}O_5$ requires; 201.0763). ^1H NMR (D_2O): δ 4.21 (1H, *br d*, *J* = 14.5 Hz, H-10a), 4.07 (1H, *br d*, *J* = 14.5 Hz, H-10b), 3.93 (1H, *dd*, *J* = 4.5, 2.6 Hz, H-6), 3.42 (2H, *t*, *J* = 6.7 Hz, H-3), 2.64 (1H, *dd*, *J* = 17.0, 4.6 Hz, H-7a), 2.59 (1H, *m*, H-5), 2.05 (1H, *d*, *J* = 17.0 Hz, H-7b), 1.62 (1H, *dt*, *J* = 12.8, 6.7 Hz, H-4a), 1.44 (1H, *dt*, *J* = 12.8, 6.7 Hz, H-4b). ^{13}C NMR: Table 1.

Crescentin III (**3**). Powder; $[\alpha]_D^{25}$ −55° (MeOH; *c* 0.6). FAB-MS (negative): *m/z* 307. 1171 $[M-H]^-$ ($C_{16}H_{19}O_6$ requires; 307.1182). ^1H NMR (pyridine-d_5): δ 8.20 (2H, *d*, *J* = 8.8, H-2′, 6′), 7.09 (2H, *d*, *J* = 8.8 Hz, H-3′, 5′), 5.92 (1H, *ddd*, *J* = 6.6, 6.3, 1.9 Hz, H-6), 4.77 (1H, *d*, *J* = 12.4 Hz, H-10a), 4.59 (2H, *br s*, H-1), 4.57 (1H, *d*, *J* = 12.4 Hz, H-10b), 4.14 (1H, *ddd*, *J* = 12.7, 7.1, 6.3 Hz, H-3a), 4.11 (1H, *ddd*, *J* = 12.7, 7.1, 6.3 Hz, H-3b), 3.68 (1H, *ddd*, *J* = 7.8, 7.3, 6.6 Hz, H-5), 3.16 (1H, *dd*, *J* = 15.1, 6.3 Hz, H-7a), 3.01 (1H, *dd*, *J* = 15.1, 1.9 Hz, H-7b), 2.49 (1H, *dddd*, *J* = 12.4, 7.3, 7.1, 6.3 Hz, H-4a), 2.45 (1H, *dddd*, *J* = 12.4, 7.8, 7.1, 6.3 Hz, H-4b). ^{13}C NMR: Table 1.

Crescentin IV (**4**). Oil; $[\alpha]_D^{25}$ −39° (MeOH; *c* 0.5). FAB-MS (negative): *m/z* 189.1142 $[M-H]^-$ ($C_9H_{17}O_4$ requires; 189.1127). ^1H NMR (D_2O): δ 3.96 (1H, *ddd*, *J* = 8.1, 5.1, 3.8 Hz, H-6), 3.52 (4H, H-1a, 1b, 3a, 3b), 2.23 (1H, *dddd*, *J* = 9.1, 6.7, 3.8, 2.7 Hz, H-5), 2.17 (1H, *dd*, *J* = 14.2, 8.1 Hz, H-7a), 2.15 (1H, *ddd*, *J* = 11.4, 9.1, 3.6 Hz, H-9), 1.66 (1H, *dd*, *J* = 14.2, 5.1 Hz, H-7b), 1.62 (1H, *dt*, *J* = 13.7, 6.7 Hz, H-4a), 1.44 (1H, *ddd*, *J* = 13.7, 6.6, 2.7 Hz, H-4b), 1.20 (3H, *s*, H-10). ^{13}C NMR: Table 1.

Crescentoside A (**12**). Powder; $[\alpha]_D^{25}$ −21° (MeOH; *c* 0.7). FAB-MS (negative): *m/z* 331.1409 $[M-H]^-$ ($C_{15}H_{23}O_8$ requires; *m/z* 331.1393). ^1H NMR (D_2O): δ 5.50 (1H, *br s*, H-7), 4.96 (1H, *br d*, *J* = 7.6 Hz, H-6), 4.28 (1H, *d*, *J* = 7.8 Hz, Glc-H-1), 4.01 (1H, *d*, *J* = 14.9 Hz, H-10a), 3.96 (1H, *d*, *J* = 14.9 Hz, H-10b), 3.75 (1H, *dd*, *J* = 12.0, 1.8 Hz, Glc-H-6a), 3.66 (1H, *dd*, *J* = 12.0, 5.6 Hz, H-1a), 3.60 (1H, *ddd*, *J* = 12.8, 6.6, 4.4 Hz, H-3a), 3.55 (2H, *m*, H-3b, Glc-H-6b), 3.49 (1H, *dd*, *J* = 12.0, 9.0 Hz, H-1b), 3.39 (1H, *dd*, *J* = 8.8, 8.8 Hz, Glc-H-3), 3.35 (1H, *ddd*, *J* = 8.8, 5.7, 1.8 Hz, Glc-H-5), 3.24 (1H, *dd*, *J* = 8.8, Hz, Glc-H-4), 3.14 (1H, *dd*, *J* = 8.8, 7.8 Hz, Glc-H-2), 3.08 (1H, *dddd*, *J* = 7.8, 7.6, 7.2, 6.8 Hz, H-5), 2.96 (1H, *ddd*, *J* = 9.0, 7.8, 5.6 Hz, H-9), 1.74 (1H, *m*, H-4a), 1.72 (1H, *m*, H-4b). ^{13}C NMR: Table 1.

Crescentin V (**13**). Powder; $[\alpha]_D^{22}$ −53° (MeOH; *c* 0.5). FAB-MS (negative): *m/z* 167.0681 $[M-H]^-$ ($C_9H_{11}O_3$ requires; *m/z* 167.0708). ^1H NMR (D_2O): δ 6.21 (1H, *d*, *J* = 6.6 Hz, H-3), 5.81 (1H, *br s*, H-7), 4.79 (1H, *dd*, *J* = 6.6, 4.6 Hz, H-4), 4.96 (1H, *br d*, *J* = 7.6 Hz, H-6), 3.98 (1H, *d*, *J* = 14.0 Hz, H-10a), 3.95 (1H, *d*, *J* = 14.0 Hz, H-10b), 3.66 (1H, *dd*, *J* = 12.1, 5.6 Hz, H-1a), 3.49 (1H, *dd*, *J* = 12.1, 9.0 Hz, H-1b), 3.08 (1H, *ddd*, *J* = 7.8, 7.6, 7.2, 6.8 Hz, H-5), 2.96 (1H, *ddd*, *J* = 9.0, 7.8, 5.6 Hz, H-9). ^{13}C NMR: Table 1.

Crescentoside B (**14**). Powder; $[\alpha]_D^{25}$ −43° (MeOH; *c* 0.5). FAB-MS (negative): *m/z* 329.1251 $[M-H]^-$ ($C_{15}H_{21}O_8$ requires; *m/z* 329.1236). ^1H NMR (D_2O): δ 6.21 (1H, *d*, *J* = 6.6 Hz, H-3), 5.81 (1H, *br s*, H-7), 4.96 (1H, *br d*, *J* = 7.6 Hz, H-6), 4.79 (1H, *dd*, *J* = 6.6, 4.6 Hz, H-4), 4.35 (1H, *d*, *J* = 8.0 Hz, Glc-H-1), 3.98 (1H, *d*, *J* = 14.0 Hz, H-10a), 3.95 (1H, *d*, *J* = 14.0 Hz, H-10b), 3.76 (1H, *dd*, *J* = 12.0, 1.8 Hz, Glc-H-6a), 3.66 (1H, *dd*, *J* = 12.0, 5.6 Hz, H-1a), 3.56 (1H, *dd*, *J* = 12.0, 4.9 Hz, Glc-H-6b), 3.49 (1H, *dd*, *J* = 12.0, 9.0 Hz, H-1b), 3.40 (1H, *dd*, *J* = 9.0, 9.0 Hz, Glc-H-3), 3.35 (1H, *ddd*, *J* = 9.0, 4.9, 1.8 Hz, Glc-H-5), 3.26 (1H, *dd*, *J* = 9.0, 9.0 Hz, Glc-H-4), 3.15 (1H, *dd*, *J* = 9.0, 8.0 Hz, Glc-H-2), 3.04 (1H, *ddd*, *J* = 9.0, 7.8,

Table 1. ^{13}C NMR data of compounds **1–4** and **11–16** in D_2O

C	1	2	3*	4	11	12	13	14	15	16
1	175.4	175.0	56.9	57.8	67.0	66.9	67.3	67.1	93.0	92.8
3	59.6	59.5	61.1	60.5	58.9	58.8	142.0	141.8	94.8	94.2
4	33.2	33.5	31.3	30.4	26.8	27.1	105.6	105.3	32.4	27.9
5	52.2	52.2	47.1	44.2	41.9	42.0	39.8	39.8	32.6	28.4
6	74.5	74.1	75.8	75.8	86.6	86.5	86.9	87.1	138.2	60.8
7	45.4	45.3	41.0	47.9	124.8	124.8	124.7	124.7	132.1	59.1
8	141.3	145.8	136.9	78.8	148.0	146.9	147.8	147.0	83.1	78.4
9	133.7	133.5	139.2	52.4	47.3	46.0	47.0	46.1	50.3	43.6
10	14.5	60.9	58.4	23.5	60.5	68.7	60.3	68.7	65.2	62.4
1′			122.1							
2′,6′			132.3							
3′, 5′			116.1							
4′			163.5							
C = O			166.5							
Glc-1						100.1		99.9	97.2	97.2
-2						72.6		72.6	72.3	72.2
-3						75.5		75.5	75.7	75.8
-4						69.2		69.1	69.2	69.2
-5						75.3		75.3	75.2	75.2
-6						60.3		60.2	60.3	60.2

* In pyridine-d_5.

5.6 Hz, H-9), 2.70 (1H, *ddd*, J = 7.8, 7.6, 4.6 Hz, H-5). ^{13}C NMR: Table 1.

Crescentoside C (**15**). Powder; $[\alpha]_D^{27} -33°$ (MeOH; *c* 0.9). FAB-MS (negative): *m/z* 345.1201 $[M-H]^-$ ($C_{15}H_{21}O_9$ requires; 345.1186). ^1H NMR (D_2O): δ 6.05 (1H, *dd*, J = 5.6, 3.4 Hz, H-6), 5.59 (1H, *br s*, H-1), 5.49 (1H, *d*, J = 5.6 Hz, H-7), 5.23 (1H, *br s*, H-3), 4.73 (1H, *d*, J = 8.1 Hz, Glc-H-1), 3.79 (1H, *dd*, J = 12.4, 3.7 Hz, Glc-H-6a), 3.64 (1H, *d*, J = 12.0 Hz, H-10a), 3.59 (1H, *dd*, J = 12.4, 5.6 Hz, Glc-H-6b), 3.40 (1H, *t*, J = 9.0 Hz, Glc-H-3), 3.38 (1H, *d*, J = 12.0 Hz, H-10b), 3.35 (1H, *ddd*, J = 9.0, 5.6, 3.7 Hz, Glc-H-5), 3.24 (1H, *t*, J = 9.0 Hz, Glc-H-4), 3.16 (1H, *dd*, J = 9.0, 8.1 Hz, Glc-H-2), 2.86 (1H, *ddd*, J = 8.8, 6.8, 3.4 Hz, H-5), 2.40 (1H, *d*, J = 6.8 Hz, H-9), 2.13 (1H, *dd*, J = 14.8, 8.8 Hz, H-4a), 1.59 (1H, *br d*, J = 14.8 Hz, H-4b). ^{13}C NMR: Table 1.

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