Notes

New Type of Mono-tetrahydrofuran Ring Acetogenins from *Goniothalamus donnaiensis*

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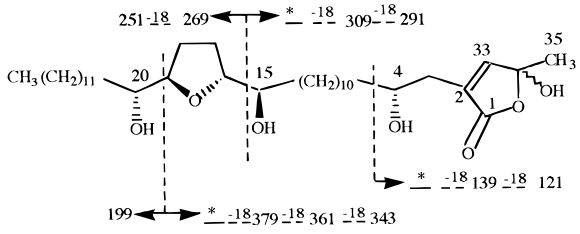
A new type of Annonaceous acetogenin was isolated from the roots of *Goniothalamus donnaiensis*. The structures of two epimeric pairs, donnaienin A (**1**) and 34-*epi*-donnaienin A (**1′**), and donnaienin B (**2**) and 34-*epi*-donnaienin B (**2′**), characterized by the presence of a γ-(hydroxymethyl) γ-lactone moiety, were elucidated by spectroscopic analysis and chemical derivatization. Four known mono-THF acetogenins—murisolin, isoannonacin, and a mixture of annonacin and goniothalamicin—were also isolated.

In recent years, nearly 200 acetogenins have been isolated from several genera of the Annonaceae.[1] Five types of terminal lactones have been reported.[2−4] From the roots of *Goniothalamus donnaiensis* Finet et Gagnep, we have isolated two novel epimeric pairs belonging to a new subclass of the acetogenins, characterized by the presence of a γ-(hydroxymethyl) γ-lactone, namely, donnaienin A (**1**) and 34-*epi*-donnaienin A (**1′**) and donnaienin B (**2**) and 34-*epi*-donnaienin B (**2′**).

Donnaienin A (**1**) and 34-*epi*-donnaienin A (**1′**), like some similar lactol compounds,[5] were isolated as an epimeric pair. High-performance TLC (Si gel), developed with different solvents, always afforded one spot, and repeated reversed-phase and normal-phase HPLC similarly gave a sharp single peak. MS and elemental analysis indicated a molecular formula of $C_{35}H_{64}O_7$ and an identical carbon skeleton for **1** and **1′** (Figure 1). However, the ^{13}C-NMR spectrum revealed a duplication of several signals that appeared at δ 69.3/71.2, 104.9/105.2, 131.8/132.5, 150.5/149.4, and 171.9/172.8, with a relative intensity of 55/45 for all of these, suggesting the presence of two epimeric compounds. ^{1}H-NMR, ^{1}H−^{1}H COSY, and ^{1}H−^{13}C COSY indicated that the chemical shifts of protons H-3 and H-4 were obviously different for **1** and **1′**. H-3a and H-3b of **1** were observed at δ 2.26 (dq) and 2.52 (dd), respectively, correlating with the ^{13}C-NMR signal at δ 33.0; H-4 of **1** was at δ 3.91 (m) and correlated with the ^{13}C-NMR signal at δ 69.3. In the case of **1′**, H-3a and H-3b resonated at δ 2.42 (m), correlating with the carbon at δ 32.0; H-4 appeared at δ 3.77 (m), correlating with the carbon at δ 71.2. In the HMBC spectrum, the carbon chemical shift at δ 69.3 correlated with the protons resonating at δ 2.26 and 2.52, while the carbon that appeared at δ 71.2 correlated with the protons at δ 2.42. Accordingly, it was possible to assign the NMR spectra for **1** and **1′** (Table 1). Several spectral characteristics in the γ-lactone moiety of **1** and **1′** clearly distinguished them from any previously known acetogenins. First, in the ^{1}H-NMR spectrum, the H-34 signal (ca. δ 5.04 or 4.50) disappeared, and the H-35 protons exhibited a signal at δ 1.66 (s) instead of δ 1.42 (d). Second, in the ^{13}C-NMR spectrum, the signals at δ 104.9/105.2 (C-34) replaced the signal around δ 77.9 (or 82.5). These data indicated that for **1** and **1′**, H-34 was substituted by a hydroxy group, and this was confirmed by a DEPT experiment that indicated that C-34 of **1** (**1′**) was a quaternary carbon.



* Ions not observed

Figure 1. Diagnostic EIMS fragment ions (m/z) of compounds **1** and **1′**.

In order to confirm that **1** and **1′** were epimeric at C-34, a phenylhydrazone derivative (**3**) was prepared.[6] In the ^{13}C-NMR spectrum of **3**, all the signals appeared to be singlets, suggesting it was one compound. In its ^{1}H-NMR spectrum, the signals of H-4, H-3a, and H-3b appeared at δ 3.90 (m), 2.70 (dq), 2.86 (dd), respectively (Table 1). The EIMS of **3** and of its TMSi derivative (**3a**) further confirmed the structures of **1** and **1′** (Figure 2).

The relative configurations of the tetrahydrofuran (THF) system of **1** and **1′** were assigned as *threo*/*trans*/*threo* by ^{1}H- and ^{13}C-NMR.[7,8] The absolute stereochemistry of C-4, C-15, and C-20 was assigned by studying the per-Mosher ester derivatives (**3s** and **3r**) of **3**.[9] The ^{1}H-NMR chemical shift data of **3s** and **3r** showed that the signs for $\Delta\delta_{S-R}$ of H-3, H-33, and H-35 were negative, indicating the C-4*R* configuration in **1** and **1′**. This result is identical to all acetogenins examined so far that possess an OH at C-4. Similarly, the Mosher ester data showed that the optical signs for $\Delta\delta_{S-R}$ of H-16, H-17, H-18, and H-19 were negative. These allowed the absolute stereochemical assignment of the carbinol centers adjacent to the mono-THF ring in **1** and **1′** as C-15*R* and C-20*R* (Table 2).

Donnaienin B (**2**) and 34-*epi*-donnaienin B (**2′**) were also obtained as an epimeric pair, and they gave only

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Table 1. ^{1}H- (500 MHz) and ^{13}C- (125 MHz) NMR Resonances (δ) for Compounds **1**, **1′**, and **3**

	1		**1′**		**3**	
position	δ ^{1}H (J in Hz)	δ ^{13}C	δ ^{1}H (J in Hz)	δ ^{13}C	δ ^{1}H (J in Hz)[a]	δ ^{13}C[b]
1		171.9		172.8		161.5
2		131.8		132.5		131.9
3a	2.26, dq (14.1, 9.3)	33.0	2.42, m	32.0	2.70, dq (13.9, 8.2)	33.4
3b	2.52, dd (14.1, 4.2)		2.42, m		2.86, dd (13.9, 4.0)	
4	3.91, m	69.3	3.77, m	71.2	3.90, m	70.8
5−14	1.2−1.6, m	22−38	1.2−1.6, m	22−38	1.2−1.6, m	22−40
15	3.41, m	74.4[c]	3.41, m	74.4[d]	3.40, m	74.0[e]
16	3.77, m	82.6	3.77, m	82.6	3.80, m	82.7
17a,b	1.97, m	28.8	1.97, m	28.8	1.97, m	28.7
	1.62, m		1.62, m		1.62, m	
18a,b	1.97, m	28.8	1.97, m	28.8	1.97, m	28.7
	1.62, m		1.62, m		1.62, m	
19	3.77, m	82.6	3.77, m	82.6	3.80, m	82.7
20	3.41, m	74.3[c]	3.41, m	74.3[d]	3.40, m	74.3[e]
21−31	1.2−1.6, m	22−38	1.2−1.6, m	22−38	1.2−1.6, m	22−40
32	0.88, t (6.8)	14.0	0.88, t (6.8)	14.0	0.88, t (6.8)	14.0
33	6.96, s	150.5	6.96, s	149.4	7.07, s	141.7
34		104.9		105.2		145.3
35	1.66, s	24.2	1.66, s	24.2	2.37, s	20.9

[a] Aromatic signals: δ 7.37 (1H, t), 7.46 (2H, t), 7.56 (2H, d). [b] Aromatic signals: δ 125.6 (2C), 128.2 (1C), 128.8 (2C), 142.0 (1C). [c−e] Assignments with same superscript may be interchangeable.

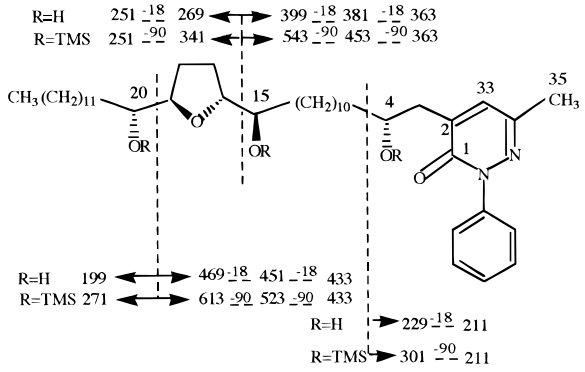

Figure 2. Diagnostic EIMS fragment ions (m/z) of compounds **3** and **3a**.

Table 2. ^{1}H-NMR Chemical Shift Data (δ) for the Determination of the Absolute Configuration of Compound **3** from Its (*S*)- and (*R*)-MTPA Mosher Ester Derivatives

MTPA deriv	MTPA confign	proton chemical shifts ($\Delta\delta = \delta_s - \delta_r$) H-4	H-3	H-33	H-35	carbinol confign at C-4
3	*S*	5.53	2.69, 3.05	6.76	2.19	
	R	5.53	2.76, 3.09	6.92	2.23	*R*
	$\Delta\delta$		−(0.07, 0.04)	−(0.16)	−(0.04)	

MTPA deriv	MTPA confign	proton chemical shifts ($\Delta\delta = \delta_s - \delta_r$) H-20	H-19	H-18, H-17	H-16	H-15	at C-15 and C-20
3	*S*	4.96	3.92	1.78, 1.40	3.92	4.96	
	R	5.02	4.00	1.92, 1.49	4.00	5.02	*R*
	$\Delta\delta$		−(0.08)	−(0.14, 0.09)	−(0.08)		

one spot by high-performance TLC with different solvents. Repeated reversed-phase and normal-phase HPLC also gave one sharp peak in each case. MS and elemental analysis indicated a molecular formula of $C_{35}H_{64}O_8$ and an identical carbon skeleton. Similar to **1** and **1′**, the ^{1}H- and ^{13}C-NMR spectra of **2** and **2′** also showed the duplication of several signals with a ratio of 55/45, suggesting they were epimeric at C-34. This suggestion was confirmed by the formation of a phenylhydrazone derivative (**4**). The NMR spectra of the mixture of **2** and **2′** and **4** (Table 3) indicated that **2** and **2′** are mono-THF acetogenins with a single hydroxyl group adjacent to the THF ring.[10] The positions of the THF ring and the OH groups were established by EIMS of **2** and **2′** (Figure 3), and further confirmed by the analogous EIMS fragmentations of **4** and its per-TMSi derivative (**4a**) (Figure 4).

The relative stereochemistry between C-13 and C-14 of **2** and **2′** was determined as *threo* by comparing the ^{13}C-NMR signal of the hydroxylated carbon C-14 (δ 74.7) and the ^{1}H-NMR signals of H-13 (δ 3.80) and H-14 (δ 3.40) with those of model compounds of known relative stereochemistry.[7] The ether proton H-13 of **2** and **2′** resonated at δ 3.80, also suggesting the existence of a *trans*-THF ring in **2** and **2′**.[11] The formation of an acetonide **4b** from **4** provided further evidence that a 1,2-diol was present in **2** and **2′**. The acetonyl methyls appeared at δ 1.367, and the dioxolane ring protons appeared at δ 3.60, indicating that the 1, 2-diol has a *threo* configuration.[12,13]

The absolute stereochemistry of C-4 and C-14 in **2** and **2′** was assigned by the preparation of the per-Mosher ester derivatives (**4bs** and **4br**) of **4b**. The ^{1}H-NMR data of **4bs** and **4br** (Table 4) indicated C-4*R* and C-14*S* configurations. Consequently, C-13 and C-10 were concluded to have the respective *S* and *R* configurations in both **2** and **2′**. The H-14 signal in **4b** showed a quartet pattern at δ 3.40, indicating that the *threo* diol at C-17, C-18 has the *S*,*S* configuration.[11,14]

The mixture of epimers of **1** and **1′** showed potent cytotoxcity against KB (human nasopharyngeal carcinoma) (IC_{50} < 1 μg/mL) and HCT-8 (human colon adenocarcinoma) cells (IC_{50} < 10 μg/mL); the mixture of epimers of **2** and **2′** was also cytotoxic to KB cells (53.8% inhibition, 10 μg/mL).

Experimental Section

General Experimental Procedures. Melting point determinations were made on a Boetius micromelting point apparatus and are uncorrected. Optical rotation determinations were made on a Perkin-Elmer 241 polarimeter. UV spectra were measured on a Shimadzu UV-240 spectrometer. IR spectra were measured on a Perkin-Elmer 683 spectrometer. ^{1}H-NMR, COSY, and ^{13}C-NMR spectra were obtained on a Bruker AM-500 spectrometer. MS spectra were obtained on a ZAB-2F

Table 3. ^{1}H- (500 MHz) and ^{13}C- (125 MHz) NMR Resonances (δ) for Compounds **2**, **2′**, **4**, and **4b**

	2		**2′**		**4**	**4b**	
position	δ ^{1}H (J in Hz)	δ ^{13}C	δ ^{1}H (J in Hz)	δ ^{13}C	δ ^{1}H (J in Hz)[a]	δ ^{13}C[b]	δ ^{1}H (J in Hz)[c]
1		171.8		172.5		161.5	
2		131.9		132.4		132.0	
3a	2.26, dq (14.1, 9.3)	33.0	2.41, m	32.1	2.69, dq (13.9, 8.2)	33.2	2.69, dq (13.9, 8.2)
3b	2.52, dd (14.1, 4.2)		2.41, m		2.85, dd (13.9, 4.0)		2.85, dd (13.9, 4.0)
4	3.91, m	68.9	3.80, m	70.8	3.91, m	70.7	3.89, m
5−9	1.2−1.6, m	22−38	1.2−1.6, m	22−38	1.2−1.6, m	22−40	1.2−1.6, m
10	3.91, m	79.6	3.91, m	79.4	3.91, m	79.3	3.89, m
11a,b	2.00, m	32.4	2.00, m	32.4	2.00, m	32.4	2.00, m
	1.60, m		1.60, m		1.60, m		1.60, m
12a,b	2.00, m	28.5	2.00, m	28.5	2.00, m	28.4	2.00, m
	1.60, m		1.60, m		1.60, m		1.60, m
13	3.80, m	82.0	3.80, m	82.0	3.78, m	8.18	3.80, m
14	3.41, m	7.47[d]	3.41, m	74.7[e]	3.40, m	74.7[f]	3.42, m
15−16	1.2−1.6, m	33−35	1.2−1.6, m	33−35	1.2−1.6, m	33−38	1.2−1.6, m
17	3.41, m	74.3[d]	3.41, m	74.3[e]	3.40, m	74.4[f]	3.60, m
18	3.41, m	74.2[d]	3.41, m	74.2[e]	3.40, m	74.3[f]	3.60, m
19−31	1.2−1.6, m	22−38	1.2−1.6, m	22−38	1.2−1.6, m	22−40	1.2−1.6, m
32	0.88, t (6.8)	14.0	0.88, t (6.8)	14.0	0.87, t (6.8)	14.1	0.87, t (6.8)
33	6.97, s	150.6	6.95, s	149.5	7.07, s	141.6	7.07, s
34		105.0		105.2		145.3	
35	1.66, s	24.2	1.66, s	24.2	2.37, s	20.9	2.37, s

[a] Aromatic signals: δ 7.37 (1H, t), 7.46 (2H, t), 7.56 (2H, d). [b] Aromatic signals: δ 125.6 (2C), 128.2 (1C), 128.8 (2C), 142.0 (1C) [c] Aromatic signals: δ 7.37 (1H, t), 7.46 (2H, t), 7.56 (2H, d); acetonyl methyl signal: δ 1.37 (6H, s). [d−f] Assignments with same superscript may be interchangeable.

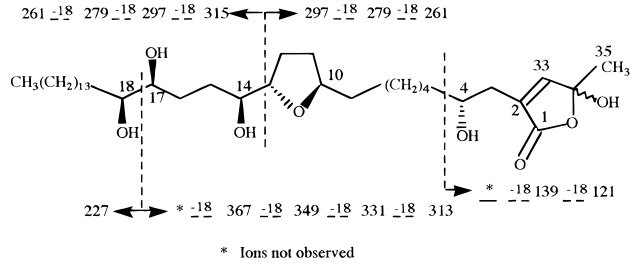

Figure 3. Diagnostic EIMS fragment ions (m/z) of compounds **2** and **2′**.

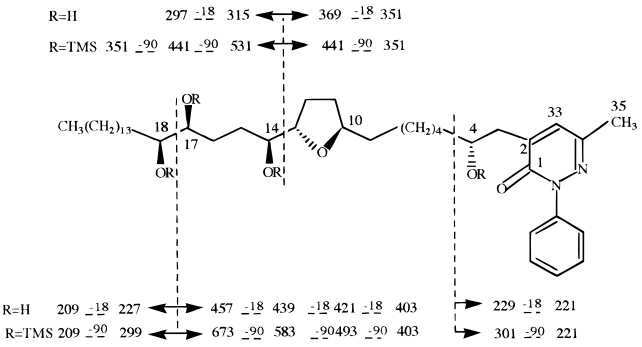

Figure 4. Diagnostic EIMS fragment ions (m/z) of compounds **4** and **4a**.

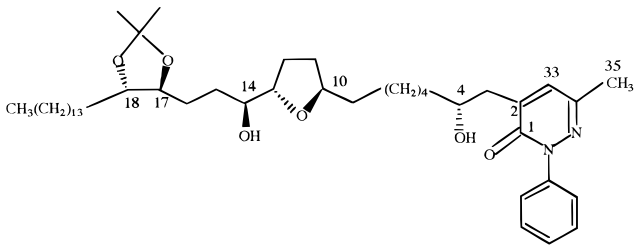

Figure 5. Structure of compound **4b**.

spectrometer. Elemental analysis was performed on a MOD1106 elemental analyzer. Gilson Model 303 pumps and a Gilson Model 116 ultraviolet detector were used in HPLC detection.

Si gel (120−180 mesh), purchased from Qing-dao Marine Chemical Factory (Qingdao City, Shangdong Province, People's Republic of China), was used for column chromatography. Si gel GF_{254} (40-μm diameter) was used for preparative and analytical TLC. TLC plates were visualized by spraying with 5% H_2SO_4 in EtOH, followed by heating. Normal-phase analytical HPLC runs were obtained using a Dupont column packed with Zorbaxsil 7-μm Si gel. Reversed-phase HPLC was performed on a column packed with Nucleosil 7-μm C_{18} Si gel.

Plant Material. The dried roots (9.5 kg) of *G. donnaiensis* Finet et Gagnep (Annonaceae) were collected from Long Jin County, Guangxi Province, People's Republic of China, in August 1994, and a voucher specimen of the plant has been deposited at the Department of Medicinal Plants, Guangxi College of Traditional Chinese Medicine. The plant material was pulverized using an electric mill.

Biological Evaluation. Five-day cytotoxicity tests of the isolated compounds against human solid tumor cell lines were performed at the Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences, using the KB nasopharyngeal carcinoma and HCT-8 colon adenocarcinoma cell lines.

Extraction and Isolation. The pulverized roots of *G. donnaiensis* (9.5 kg) were exhaustively extracted with 95% EtOH to yield extract F001 (2.05 kg), which was partitioned between H_2O and $CHCl_3$ (1:1), giving the H_2O-soluble fraction F002 (448 g) and the $CHCl_3$-soluble fraction F003 (820 g). F003 was then partitioned between 90% aqueous MeOH and petroleum ether (1:1) to yield the petroleum ether-soluble fraction F006 (42 g) and the aqueous MeOH-soluble fraction F005 (638 g). F005 (91 g) was applied to a column of Si gel (120−180 mesh), eluted with $CHCl_3$ containing gradually increasing proportions of MeOH. Impure components were combined according to their similar appearance on TLC analysis, and these were again subjected to repeated chromatography to yield the crude compounds **1** (**1′**) and **2** (**2′**). These were then purified by preparative TLC, developed with $CHCl_3$−MeOH (93:7) and

Table 4. ^{1}H-NMR Chemical Shift Data (δ) for the Determination of the Absolute Configuration of Compound **4b** from Its (*S*)- and (*R*)-MTPA Mosher Ester Derivatives

MTPA deriv	MTPA confign	proton chemical shifts ($\Delta\delta = \delta_s - \delta_r$) H-4	H-3	H-33	H-35	carbinol confign at C-4
4b	*S*	5.53	2.68, 3.03	6.76	2.19	
	R	5.53	2.75, 3.08	6.91	2.23	*R*
	$\Delta\delta$		−(0.07, 0.05)	−(0.15)	−(0.04)	

MTPA deriv	MTPA confign	proton chemical shifts ($\Delta\delta = \delta_s - \delta_r$) Acetonyl Methyls	H-18, H-17	H-14	H-13	H-12	H-11	H-10	carbinol confign at C-14
4b	*S*	1.33, 1.34	3.44, 3.48	5.07	4.02	2.00, 1.69	2.00, 1.75	3.87	
	R	1.37, 1.39	3.57, 3.59	5.09	4.01	1.86, 1.67	1.92, 1.74	3.76	*S*
	$\Delta\delta$	−(0.04, 0.05)	−(0.13, 0.11)		+(0.01)	+(0.14, 0.02)	+(0.08, 0.01)	+(0.11)	

hexane−EtOAc−MeOH (6:3:1), respectively, to afford the two amorphous powders **1** (**1′**) and **2** (**2′**). Using the same methods, four known compounds (murisolin, isoannonacin, and a mixture of annonacin and goniothalamicin) were also obtained. The two epimers **1** (**1′**) and **2** (**2′**), when run on reversed-phase and normal-phase HPLC with different solvent systems, gave a sharp single peak in all cases.

Donnaienin A (1) and 34-*epi*-donnaienin A (1′): white, amorphous powder from hexane−EtOAc (1:4), 88 mg; mp 96−98 °C, $[\alpha]^{18}_D$ −7.6° (*c* 0.07, $CHCl_3$); UV (MeOH) λ max 205 (ϵ 6831), 248 sh (ϵ 1192) nm; IR ν max 3390 (OH), 2920 and 2850 (CH), 1762 (lactone C=O), 1467 (CH) cm^{-1}; ^{1}H-NMR data, see Table 1; ^{13}C-NMR data, see Table 1; FABMS *m*/*z* $[M + Na]^+$ 619 (40); EIMS *m*/*z* $[MH]^+$ 597 (0.2), 579 (2), 561 (2), 543 (3), 525 (2), 379 (3), 361 (28), 343 (12), 309 (100), 291 (15); *anal*. C 70.53%, H 10.97%, calcd for $C_{35}H_{64}O_7$, C 70.47%, H 10.74%.

Donnaienin B (2) and 34-*epi*-donnaienin B (2′): white, amorphous powder from EtOAc, 76 mg; mp 70−72 °C, $[\alpha]^{30}_D$ −19.0° (*c* 0.09, MeOH); UV (MeOH) λ max 208 (ϵ 6815), 250 sh (ϵ 1180) nm; IR ν max 3395 (OH), 2923 and 2852 (CH), 1752 (lactone C=O), 1465 (CH); ^{1}H-NMR data, see Table 3; ^{13}C-NMR data, see Table 3; FABMS *m*/*z* $[M + Na]^+$ 635 (35); CIMS *m*/*z* $[MH - H_2O]^+$ 595 (8), 577 (23), 559 (100), 541 (38), 523 (25); EIMS *m*/*z* 367 (2), 349 (50), 331 (30), 313 (8), 297 (20), 297 (82), 261 (10); *anal*. C 68.58%, H 10.42%, calcd for $C_{35}H_{64}O_8$, C 68.63%, H 10.46%.

Phenylhydrazone Derivatives of 1 (1′) and 2 (2′). In each case, a mixture of a 20-mg sample and 5 mg of phenylhydrazine in 10 mL of EtOH was refluxed for 2 h. The viscous mass (**3** or **4**) which was produced after removal of solvent *in vacuo* was purified by preparative TLC. Compound **3** was obtained as a white powder: ^{1}H-NMR (500MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$) data, see Table 1; EIMS *m*/*z* 469 (30), 451 (25), 433 (10), 399 (90), 381 (35), 363 (5). Compound **4** was also obtained as a white powder: ^{1}H-NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$) data, see Table 3; EIMS *m*/*z* 457 (2), 439 (15), 421 (10), 403 (8), 369 (85), 351 (38).

TMSi Derivatives of 3 and 4. Samples of no more than 1 mg were treated with 20 μL of *N*,*O*-*bis*(trimethylsilyl)-acetamide and 2 μL of pyridine and heated at 70 °C for 30 min to yield trimethylsilyl (TMSi) ethers (**3a** and **4a**) that were analyzed by EIMS.

Acetonide Derivative of 4. To **4** (12 mg in 5 mL of CH_2Cl_2) was added 0.3 mL of 2,2-dimethoxypropane and a few of crystals of *p*-toluenesulfonic acid, and stirred at room temperature for 2 h. The product (**4b**) was purified by preparative TLC. Compound **4b**: colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) data, see Table 3.

MTPA Derivatives of 3 and 4b. (*R*)-(+)- or (*S*)-(−)-Methyl-α-(trifluoromethyl)phenylacetic acid (MTPA, 35 mg) and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 30 mg) were added to a 5-mg sample of **3** or **4b** dissolved in dry CH_2Cl_2 with a few crystals of (dimethylamino)-pyridine (DMAP). Each mixture was stirred at room temperature for 6 h, and the products (**3r**, **3s**, **4br**, and **4bs**) were purified by preparative TLC. **3r** and **3s**: colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$ referenced to TMS) data, for characteristic resonances see Table 2. **4br** and **4bs**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$ reference to TMS) data, for characteristic resonances see Table 4.

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