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Epimeric Excolides from the Stems of *Excoecaria agallocha* and Structural Revision of Rhizophorin A

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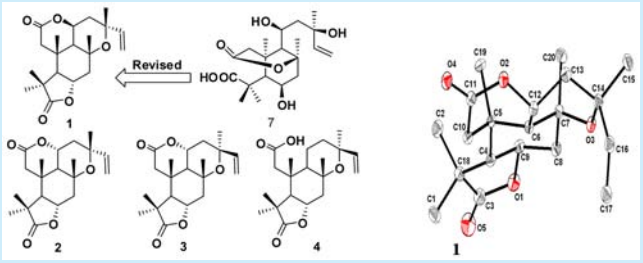
Supporting Information

ABSTRACT: Excolides A–B (**1**–**4**) represent the first examples of a new class of secolabdanoids with an unprecedented framework, which were isolated from the stems of *Excoecaria agallocha*. Their structures were determined by spectroscopic analysis, chemical modifications, CD, and single-crystal X-ray analysis (**1** and **4**) as excolide A (**1**), 11-*epi*-excolide A (**2**), 11,13-di-*epi*-excolide A (**3**), and excolide B (**4**). In addition, the structure of rhizophorin A (**7**), a novel bicyclic secolabdanoid, was revised as excolide A (**1**).



Mangroves particularly those of the genus *Excoecaria* have been recognized as a rich source of diterpenoids of structural diversity possessing a wide range of biological activities.[1,2] Of the diterpenes from the genus *Excoecaria*, most are derived from unusual assemblages with diverse classes such as labdanes, pimaranes, beyeranes, and kauranes.[3,4] As part of our ongoing research program on bioactive compounds from the Indian mangrove flora,[5−7] we have recently examined the acetone extract of the stems of *Excoecaria agallocha*, which resulted in the isolation of four new 2,3-secolabdanoids with an unprecedented skeleton: epimeric excolides A (**1**–**3**) and excolide B (**4**) along with two known compounds (Figure 1). The known compounds were characterized as excoecarin D (**5**) and agallochin I (**6**) by comparison of their physical and spectroscopic data (MS, ^{1}H and ^{13}C NMR) with reported data.[8,9]

In 2001, Anjaneyulu et al. reported the isolation of rhizophorin A, a novel bicyclic 2,3-secolabdanoid from the roots of *Rhizophora mucronata*.[10] Yet, the wrong structure was proposed due to the interpretation of CI MS and IR. It was characterized through mere spectroscopic analysis. We have revised the structure of rhizophorin A as a novel tetracyclic 2,3-secolabdanoid with bisolide termed excolide A based on spectroscopic, CD, and single crystal X-ray analyses and chemical derivatization.

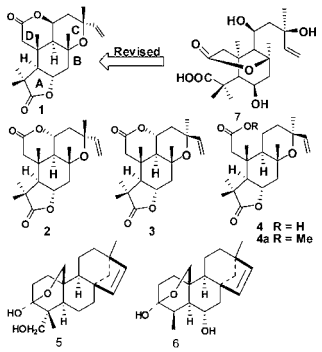


Figure 1. Compounds isolated from *Excoecaria agallocha* (**1**–**4**).

Herein, we report the isolation and structure elucidation of four novel 2,3-secolabdanoids (**1**–**4**) and the results of the cytotoxicity assay (**1**–**4**). In addition, revision of the structure of rhizophorin A (**7**) as excolide A (**1**) is described. The secolabdanoids encountered represent a unique skeleton with a tetracyclic core system. In general, labdanoids are bi-/tri-/tetracyclic in nature while 2,3-secolabdanoids with a common core tetracyclic ring system is rather unusual.

In the course of our preliminary study, **1**–**3** were first isolated as a mixture of three closely related compounds reflected by several split signals as evidenced by its ^{1}H NMR spectrum (Supporting Information (SI)). The HR-ESIMS proved that the mixture possesses three isomers with the same molecular formula, $C_{20}H_{28}O_5$. This mixture was subjected to repeated Si-gel CC (230–400 mesh), and subsequent fractional crystallization resulted in the separation of individual isomers (**1**–**3**).

Excolide A (**1**) was obtained as a white crystalline solid, mp 286 °C with optical rotation $[\alpha]_D^{25}$ +132.0 (*c* 0.1, $CHCl_3$). A molecular formula of $C_{20}H_{28}O_5$ was determined from the elemental analysis and the sodiated molecular ion peak at *m*/*z* 371.1836 $[M + Na]^+$ (calcd 371.1829 for $C_{20}H_{28}O_5Na$) in its HR-ESIMS, which was consistent with seven sites of unsaturation. Although rhizophorin A exhibited a quasimolecular ion peak at *m*/*z* 349 in its CI MS, the authors considered it as 384 $[M^+ + H -$

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Table 1. ^{1}H NMR Chemical Shifts of Compounds 1, 7,[10] 2, 3, 4 ($CDCl_3$, 600 MHz)

	1	7[10]	2	3	4
position	δ (J, Hz)	δ (J, Hz)	δ (J, Hz)	δ (J, Hz)	δ (J, Hz)
1α	2.74, d (14.6)	2.73, m	2.74, d (16.8)	2.73, d (16.8)	2.58, d (15.8)
1β	2.44, d (14.6)	2.45, m	2.43, d (16.8)	2.43, d (16.6)	2.49, d (15.8)
5	1.92, d (11.6)	1.92, d (11)	1.71, m	1.69, m	1.47, d (10.5)
6	4.40, td (11.6, 4.5)	4.40, td (11.0, 4.5)	4.28, td (11.6, 4.0)	4.25, td (11.5, 4.2)	4.28, td (12.1, 3.7)
7α	1.71, t (11.6)	1.71, t (11.6)	1.76, m	1.70, m	1.64, m
7β	2.53, dd (11.5, 4.6)	2.52, m	2.57 dd (11.8, 4.3)	2.50, dd (11.5, 4.2)	2.40, dd (11.3, 4.5)
9	2.14, d (11.1)	2.15, m	1.77, m	1.74, m	1.94, dd (11.3, 4.5)
11	4.55, ddd (12.7,11.0, 6.5)	4.55, td (14.0, 7.0)	4.82, td (11.2, 4.8)	4.71, td (11.4, 4.3)	1.65, m
12α	2.34, t (3.3)	2.35, m	1.80 m	1.70, m	1.49, m
12β	2.17, dd (11.5, 4.6)	2.17, m	2.32, dd (12.8, 4.7)	2.80, dd (12.8, 4.7)	2.27, dd (11.3, 3.0)
14	5.73, dd (16.9, 10.5)	5.73, dd (16.9, 10.5)	5.86, dd (18.0, 11.1)	6.00, dd (18.0, 11.1)	6.00, dd (17.3, 11.3)
15a	5.07, dd (10.5, 5.6)	5.07, d (10.5)	5.01, d (11.1)	5.04, d (11.1)	4.95, d (11.3)
15b	5.31, dd (16.9, 5.6)	5.31, d (16.8)	5.19, d (18.2)	5.11, d (18.2)	5.00, d (17.3)
16	1.39, s	1.38, s	1.43, s	1.26, s	1.15, s
17	1.65, s	1.64, s	1.47, s	1.36, s	1.33, s
18	1.36, s	1.35, s	1.37, s	1.38, s	1.43, s
19	1.23, s	1.23, s	1.26, s	1.24, s	1.20, s
20	1.26, s	1.25, s	1.24, s	1.18, s	0.94, s

$2H_2O$]. Further, chemical modifications on **1** with diazomethane and Ac_2O in pyridine were unsuccessful, which implied the absence of free carboxyl and acylable hydroxy groups in **1** respectively.

These results were corroborated with strong IR absorptions at 1770, 1225 cm^{-1} (γ-lactone), an additional lactone carbonyl at 1738 cm^{-1}, and ether functionality at 1150, 1063 cm^{-1}. Excolide A showed similar ^{1}H and ^{13}C NMR spectra to those of rhizophorin A (Tables 1 and 2). Alkaline hydrolysis of **1** yielded apparently a too unstable acid (**1a**), which undergoes intramolecular cyclization between C-2 and C-11 to afford excolide A as evidenced by the ^{13}C NMR. Thus, **1a** was characterized by mere ^{1}H NMR only (Figure S31).

The ^{1}H NMR spectrum of **1** (Table 1) displayed signals at δ_H 5.73 (1H, dd, J = 16.9, 10.5 Hz), 5.31 (1H, dd, J = 16.9, 5.6 Hz), and 5.07 (1H, dd, J = 10.5, 5.6 Hz) attributable to a vinyl group, five tertiary methyls, and a pair of O-bearing methines at δ_H 4.55 (1H, ddd J = 12.7, 11.0, 6.5 Hz) and δ_H 4.40 (1H, td J = 11.6, 4.5 Hz).

The ^{13}C NMR spectrum of **1** (Table 2) in $CDCl_3$ showed resonances for 20 carbons, which were differentiated by DEPT and HSQC spectra into five methyls, four methylenes, five methines, and six quaternary carbons. The presence of two carbonyls and olefinic carbons that accounted for three out of the seven double bond equivalents suggested the molecule possesses a tetracyclic core ring system. All the proton and carbon signals were assigned unambiguously from the HSQC and HMBC spectra. The aforementioned data supported the assignment of **1** as a 2,3-secolabdanoid. The multiplicity of the two oxymethine carbons indicated that they were located between a methylene and methine, possibly on C-6 and C-11 of the labdanoid. Moreover, concomitant downfield shifts of C-5 at δ 63.0 and C-1 at δ 46.1 were indicative of the oxymethine groups being located at C-6 and C-11 respectively. Further, the carbon resonances at δ 63.0 and 180.4 were assigned to the γ-lactone. The HMBC correlation of 6-H with C-4, C-5, C-7, and C-10 and a pair of *geminal* methyl groups showed a ^2J correlation to C-4 and ^3J correlations to C-3 and C-5, and IR absorptions at 1770, 1255 cm^{-1} completing ring A. **1** was found to be a 2,3-secolabdanoid with the possibility of a δ-lactone moiety between C-2 and C-11

Table 2. ^{13}C NMR Chemical Shifts of Compounds 1, 7,[10] 2, 3, 4 ($CDCl_3$, 150 MHz)

	1	7[10]	2	3	4
position	δ	δ	δ	δ	δ
1	46.1	46.3	47.2	47.4	41.9
2	171.1	170.9	167.8	167.8	174.3
3	180.4	180.5	180.4	180.4	181.4
4	43.7	43.7	43.5	43.4	43.9
5	63.0	62.9	63.0	63.0	56.6
6	74.6	74.4	73.3	73.3	74.2
7	46.3	46.1	45.6	45.7	45.5
8	74.4	74.5	75.1	75.8	75.8
9	52.5	52.4	55.2	55.9	52.2
10	36.8	36.8	35.5	35.5	39.4
11	70.8	70.7	72.0	71.9	16.2
12	36.3	36.2	44.3	41.2	34.4
13	75.1	75.0	75.6	76.0	74.1
14	143.7	143.7	145.6	146.1	146.8
15	112.9	112.9	111.5	111.0	109.7
16	30.9	30.9	28.2	32.5	32.5
17	29.0	29.0	25.6	24.6	25.9
18	25.9	25.9	25.9	25.9	24.8
19	19.3	19.2	19.9	19.9	20.2
20	20.9	20.9	17.9	17.9	20.5

but not as reported in rhizophorin A (C-2 and C-8) based on chemical modifications. **1** showed identical 2D NMR correlations to those of rhizophorin A (Table S1). In particular, the ^{1}H−^{1}H COSY cross-peaks of H-5/H-6, H-6/H-7, as well as the correlations of C-1, C-4, C-6, C-9, C-10, C-18, C-19, and C-20 with H-5; C-4, C-5, C-7, C-10 with H-6 evident in the HMBC spectrum (Figure 2; Table S2), established ring B of 2,3-secolabdanoid. Rings C and D were connected through HMBC cross peaks between 11-H/C-8, C-12; 9-H/C-5, C-7, C-10, C-17, C-20 and 16-Me/C-12, C-13, C-14. The ^{1}H−^{1}H COSY couplings between 9-H and 11-H established their relative positions. **1** possesses envelope/chair/twist-boat-like/twist-boat-like conformations for the rings A, B, C, and D respectively. The

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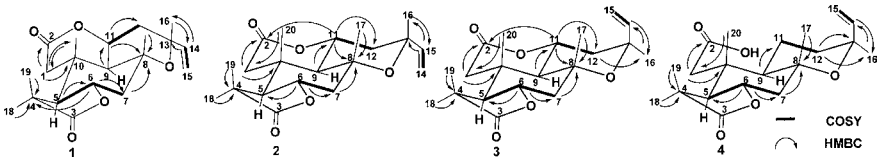

Figure 2. Key HMBC and COSY correlations of compounds **1**, **2**, **3**, and **4**.

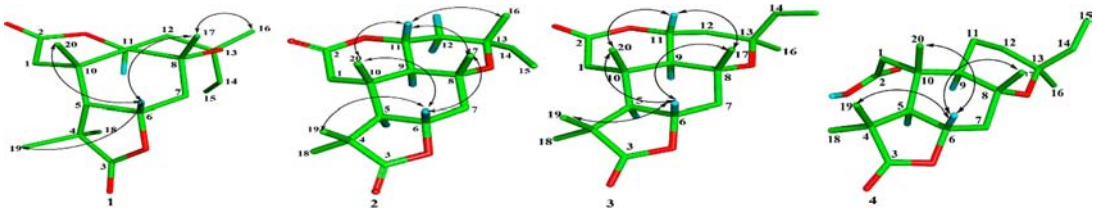

Figure 3. Key NOESY correlations of compounds **1**, **2**, **3**, and **4**.

relative stereochemistry of **1** was determined from the NOE effects (Figures S18−S22).

Irradiation of the H-6 proton caused enhancements of the H_{β}-7, 17-Me, 19-Me, and 20-Me. Consequently, the relative configurations of these methyl groups as well as H-6 are cofacial in a β-orientation (Figure 3). Unfortunately, the 1D and 2D NMR spectra did not provide enough information to establish the linkages of C-2, C-11 and C-3, C-6, but we were able to utilize chemical methods, IR, and HR-ESIMS. In order to establish the absolute stereochemistry of **1**, CD and single crystal X-ray diffraction experiments (Figure 4) were carried out. The CD

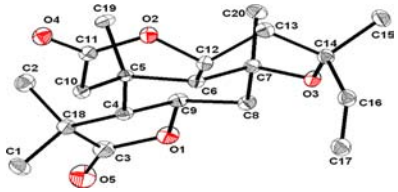

Figure 4. ORTEP drawing of compound **1**.

spectrum of **1** exhibited a positive Cotton effect at 233 nm (γ-lactone region), analogous to that of kleinhospitine B,[11] indicating the *S* absolute configuration of C-6. Furthermore, two bands in the CD spectrum were ascribed to the boat (λ < 225 nm) and twist boat conformations (λ > 230 nm).[12] X-ray diffraction analysis (CCDC 1048828) also suggested the absolute stereochemistry of **1** as 5*R*, 6*S*, 9*S*, 11*S*, 13*R*. Thus, we have revised the complete structure of bicyclic rhizophorin A as a novel tetracyclic 2,3-secolabdanoid, excolide A (8,13-epoxy-2,3-secolabd-14-en-2,11β:3,6α-diolide, **1**).

11-*epi*-Excolide A (**2**) was obtained as a crystalline solid, mp 232 °C with optical rotation $[\alpha]_D^{25}$ +106.0 (*c* 0.1, $CHCl_3$). It was analyzed and its composition was deduced as $C_{20}H_{28}O_5$ by a sodiated molecular ion peak at *m*/*z* 371.1837 $[M + Na]^+$ (calcd 371.1829), which was found to be the same as that of **1**. The ^1H and ^{13}C NMR spectroscopic data of **2** (Tables 1 and 2) were strikingly similar to those of **1**. These similarities, together with the fact that **1** and **2** possess identical molecular formulas suggested a close relationship between the two compounds. A vinyl group, two lactone carbonyl groups (at δ_C 180.4 and 167.8; IR 1771 and 1730 cm^{-1}), two oxymethines (at δ_H 4.82, 4.28 and δ_C, 73.3, 72.0) were analogous to excolide A. These data led to the preliminary conclusion that **2** is also a secolabdanoid and accounted for three of the seven double bond equivalents, indicating the compound to be tetracyclic as **1**. After the assignment of all direct C−H bonds on HSQC, the structure of **2** was elucidated as an epimer of **1**. COSY correlations from H-5/H-6/H-7, H-9/H-11 further supported this assignment. Compound **2** possesses a common core tetracyclic structure constituted by a 5/6/6/6 ring system as excolide A.

Comparison of the ^1H NMR data of **1** and **2** showed that 5-H, 6-H, 9-H were shifted to upfield while 11-H was shifted to downfield. Minor differences were observed from the ^{13}C NMR spectrum (Table 2), except for the most distinguishable carbon signals for C-2, C-9, and C-11 at δ_C 167.8, 55.2, 72.0. Unlike excolide A, the presence of δ-lactone was confirmed by the HMBC correlations of H-11 and C-2 in **2**. The above data suggested that **2** and **1** are different in the configuration at C-11 on ring D while the configurations for rings A, B, and C remain intact. Further analysis of their 2D NMR (HSQC, HMBC, and NOESY) (Figures 2 and 3; Table S2) data revealed that the pair of epimers shared the same structure and stereochemistry of rings A−D. The NMR data from C-5, C-9, C-11, and C-17 of **2** were different from those of **1**, suggesting that **2** could be a C-11 epimer of **1**, which was further supported by diagnostic NOEs for 6-H, 11-H, and 17-CH_3 that were observed after irradiation of 20-CH_3 (Figures S39−S41). In addition, irradiation of 16-CH_3 enhanced 11-H, 12-H_{β}, and 19-CH_3, which indicated their β-orientation. The absolute conformation of C-11 of **2** could be disclosed by an empirical comparison of the CD with that of **1**. The negative Cotton effect at 199 nm of **2** was in contrast to the positive Cotton effect of **1** (201 nm). The structure of **2** was unambiguously established as 11-*epi*-excolide A (8,13-epoxy-2,3-secolabd-14-en 2,11α:3,6α-diolide, **2**).

11,13-Di-*epi*-excolide A (**3**) exhibited mp 224 °C with optical rotation $[\alpha]_D^{25}$ + 76.0 (*c* 0.1, $CHCl_3$). It possessed the molecular formula $C_{20}H_{28}O_5$, as revealed by a sodiated molecular ion peak at *m*/*z* 371.1833 $[M + Na]^+$ (calcd 371.1829), which is identical to those of **1** and **2**. The IR, CD, and NMR spectroscopic data of **3** also resembles those of **1** and **2** (Tables 1−2 and Table S2) with respect to chemical shifts, spin−spin coupling constants, while the overall spin system was found to be unchanged. Spectoscopic comparison of **3** with **2** revealed that both shared the same tetracyclic structural framework with the same substitution pattern. Careful analysis of 2D NMR (^1H−^1H COSY, HSQC, HMBC) correlations (Figures 2−3; Table S2) allowed us to conclude that its structure was similar to **2**. The ^1H and ^{13}C NMR chemical shifts from C-1 to C-15 of **3** were nearly identical with those of **2**, suggesting that **3** shared the C-6 and C-11 absolute

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configurations of **2**. This was further supported by the CD and NOE spectra (Figures S55−S59). The 1D NMR data from C-16 to C-20 of **3**, especially at C-13, were different from those of **2**, suggesting that **3** could be an epimer of **2** at C-13. This was further evidenced by the absence of NOE effects after irradiation of 16-CH_3, which indicated α-orientation of 16-CH_3. Additionally, a Drieding model study showed that **3** should adopt a *trans* fused ring system, implying α-orientation of oxymethine at C-11. Further, diagnostic NOEs for 1-H_β, 6-H, H-11, and 17-CH_3 were observed after irradiation of 20-CH_3, clearly showing β-orientation of 17-CH_3/20-CH_3. An empirical comparison of the CD spectrum of **3** with that of **2** determined the same absolute stereochemistry at C-11. Consequently, the structure of compound **3** was assigned as 11,13-di-*epi*-excolide A (13-*epi*-8,13-epoxy-2,3-secolabd-14-en-2,11α:3,6α-diolide, **3**).

Excolide B (**4**) was obtained as colorless needles, mp 242 °C with optical rotation $[\alpha]_D^{25}$ +62.0 (*c* 0.2, $CHCl_3$). It has the molecular formula $C_{20}H_{30}O_5$ on the basis of the quasimolecular ion peak at *m*/*z* 351.21660 $[M + H]^+$ calcd 351.21754 in its HR-ESIMS, suggesting six degrees of unsaturation. Comparison of the IR spectrum with those of excolides A showed a characteristic absorption peak for γ-lactone functionality at (1767, 1223 cm^{-1}) and an additional carbonyl absorption peak at (1736 cm^{-1}), which indicated the presence of another 2,3-secolabdanoid. It formed a monomethyl ester (**4a**) (Table S3) on methylation with diazomethane, confirming the existence of a free carboxyl group in **4**. From 1D NMR data it is evident that five tertiary methyls and a vinyl group were present in **4**. Unlike epimeric excolides A (**1**−**3**) it possesses one oxymethine at δ_H 4.28; δ_C 74.2 which might be located at C-6 or C-11. Careful comparison of the ^1H and ^{13}C NMR data of **4** (Tables 1 and 2) with those of excolides A (**1**−**3**) revealed that **4** shares the same tricyclic core framework (A, B, C). Moreover, **4** differed from **3** with chemical shift changes in the ^{13}C NMR spectrum observed for the carbons with upfield shifts for C-1, C-2, C-3, C-5, and C-10 due to the lack of oxygenation at C-11.

Additional information was obtained by the HMBC and the NOESY experiments. The relative configuration for the chiral carbons around the tricyclic core was established by detailed analysis of the NOESY spectrum of **4**. As shown in the NOESY data (Table S2; Figure 3), the correlations of H-6 with 7-H_β, 17-CH_3, 19-CH_3, and 20-CH_3 were all cofacial arbitrarily assigned to be β-oriented. The α-orientation of 16-CH_3 was in agreement with the NOESY correlations. To confirm compound **4** is such a novel diterpene with a completely unique skeleton, further evidence such as X-ray diffraction was necessary. After many attempts with different solvents a single crystal of **4** was finally obtained from *n*-hexane/acetone (6:4) and then analyzed by an X-ray diffraction experiment (Figure 5; CCDC 1048827). We determined the absolute stereochemistry of **4** as 5*R*, 6*S*, 9*S*, 13*R*. Consequently, **4** was determined as exolide B (2,3-seco-8,13-epoxylabd-14-en-3,6α-olide-2-oic acid, **4**).

Novel secolabdanoids (**1**−**4**) may be derived from a labdane skeleton, although Euphorbiaceae is known for *ent*-labdanoids. The coexistence of labdanes and *ent*-labdanes may occur in the same plant. A plausible biogenetic pathway of secolabdanoids (**1**−**4**) was postulated as shown in Scheme S1. These compounds were derived from the same precursor (8,13-epoxy-2-hydroxylabda-1,14-diene-3-one 7)[13] (see SI for **1**−**4**), bearing a 1,2-diketone moiety that could further undergo oxidative ring A cleavage to a dicarboxylic acid (**8**). This intermediate might be prone to form γ- and δ-lactone after selective oxidation. It was noteworthy that generation of the tricyclic and epimeric

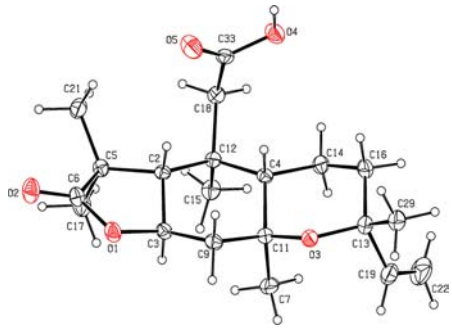

Figure 5. ORTEP drawing of compound **4**.

tetracyclic with a new skeleton appeared to depend on the selective oxidation at C-6 and C-11 followed by lactonization.

Compounds **1**−**4** were found to be inactive (IC_{50} > 10 μM) against all the human cancer cell lines tested using MTT assay (see SI).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectra (IR, HR-ESIMS, CD, 1D and 2D NMR) of **1**−**4**; ^1H NMR spectra of mixture of epimers, **1a**, and **4a**; 1D NMR of **5**; ^{13}C NMR of **6**; X-ray data of **1** and **4**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01257.

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Notes

The authors declare no competing financial interest.

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