ORGANIC LETTERS

1999
Vol. 1, No. 2
197−198

Echinothiophene, a Novel Benzothiophene Glycoside from the Roots of *Echinops grijissii*

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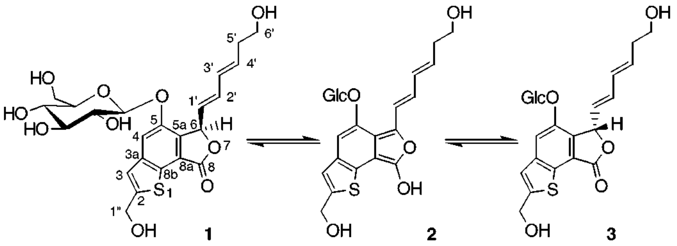
Received March 17, 1999

ABSTRACT



The structure of echinothiophene, the β-D-glucoside of a benzo[*b*]thiophene lactone bearing a novel skeleton, has been deduced from extensive NMR and MS studies. The compound undergoes facile epimerization at the C-6 center, perhaps through the enol 2. Molecular mechanics and dynamics calculations indicated that the structure 1 (C-6, *R*) is more stable than 3 (C-6, *S*).

The genus *Echinops* (Compositae) consists of ca. 100 species in the world. In China, this genus is represented by 17 species mainly distributed in the northwestern part.[1] The root of *E. grijissi* Hance (commercial name: Yuzhou Luolu) is listed in *Chinese Pharmacopeia* and is used as a remedy for different ailments.[2] Previous chemical investigation on the *Echinops* species demonstrated the presence of polyacetylene thiophenes,[3−5] alkaloids,[6] and flavone and flavone glycosides.[7] We now report the isolation and structure characterization of a novel benzo[*b*]thiophene glycoside, designated echinothiophene, from the roots of *E. grijissii*.

The *n*-BuOH-soluble fraction (20.0 g) of the defatted *E. grijissii* roots (5.0 kg) on repeated chromatographic purification over Diaion HP20, Si gel, and finally RP-HPLC gave the title compound as pale-yellowish needles (6.0 mg).[8] The IR spectrum indicated the presence of hydroxyl (3421 cm^{-1}) and γ-lactone (1750 cm^{-1}) groups while the UV spectrum suggested the presence of an aromatic chromophore in echinothiophene. The molecular formula $C_{23}H_{26}O_{10}S$ was determined from its HR FAB-MS,[8] as well as from its ^{13}C NMR spectra (Table 1). Of the 23 carbons, 17 were assigned

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(1) Shih, C. In *Flora Sinica*; Scientific Press: Beijing, 1987; Vol. 78, p 1.

(2) (a) *Chinese Pharmacopeia*; Guangdong Science and Technology Press: Suangzhou, 1995; p 229. (b) *Dictionary of Chinese Materia Medica*; Shanghai Scientific Publishing House: Shanghai, 1978; p 2576. *E. grijissii* were identified by D. Guo, and a voucher specimen was deposited at the School of Pharmaceutical Sciences, Beijing Medical University.

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(4) Guo, D.; Cui, Y.; Lou, Z.; Wang, D.; Huang, L. *Chin. Trad. Herbal Med.* **1992**, *23*, 512.

(5) Lam, J.; Christensen, L. P.; Thomason, T. *Phytochemistry* **1991**, *30*, 1157.

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(8) Echinothiophene: $C_{23}H_{26}O_{10}S$, pale-yellowish needles, mp 214−216 °C (dec), HR FAB-MS *m/z* 495.1339 $[M + H]^+$ (Δ0.0022 of the calcd) and *m/z* 517.1147 $[M + Na]^+$ (Δ0.0010 of the calcd). IR (KBr) ν_{max}cm^{-1}: 3421, 2924, 1750, 1645, 1094, 1056. UV λ_{max} nm (log ϵ): 254 (4.94), 319 (4.10).

10.1021/ol9905295 CCC: $18.00

Table 1. ^{13}C and ^{1}H NMR Data of Echinothiophene (**1**)[a]

	^{13}C	^{1}H (J in Hz)
1		
2	142.6 s	
3	119.1 d	7.36 s
3a	127.8 s	
4	116.3 d	7.88 s
5	149.3 s	
5a	137.4 s	
6	79.9 d	6.28 d (5.5)
8	168.3 s	
8a	119.0 s	
8b	154.4 s	
1′	124.6 d	6.02 dd (15.3, 5.5)
2′	131.8 d	6.39 dd (15.3, 10.6)
3′	129.9 d	6.10 dd (15.2, 10.6)
4′	133.1 d	5.79 dt (15.2, 6.7)
5′	35.5 t	2.21[b] q (6.7)
6′	60.1 t	3.44[b]q
1"	58.5 t	4.80[b] d (5.2)
Glc-1	102.2 d	4.96 d (7.6)
Glc-2	73.1 d	3.32 m
Glc-3	76.5 d	3.36 m
Glc-4	69.7 d	3.24 m
Glc-5	76.9 d	3.37 m
Glc-6	60.7 t	3.75 m, 3.53 m

[a] Recorded in DMSO-d_6 at 80 °C on a JEOL α-500 (500 MHz) spectrometer. The ^{1}H and ^{13}C assignments were based on COSY, HOHAHA, DEPT, HSQC, HMBC, and phase-sensitive NOESY. [b] 2H signal.

to the aglycon part and 6 to the carbohydrate unit, identified as glucose from the NMR data. From its NMR spectra, the aglycon moiety was found to contain two aromatic protons (δ 7.36 s, 7.88 s), two primary hydroxyl groups, and a proton attached to an oxygenated methine carbon (δ 6.28 d, $J = 5.5$ Hz). From the COSY, HOHAHA, HSQC (Table 1), and HMBC spectra, echinothiophene was concluded to possess a benzo[*b*]thiophene nucleus fused to a γ-lactone (IUPAC name: thieno[2,3-*e*]isobenzofuran-8(6*H*)-one) and a linear unsaturated primary alcohol side chain. HMBC coupling networks observed between the signals for the aromatic protons, the methine at δ 6.28 (d, $J = 5.5$ Hz), and the protons from one of the primary hydroxyl groups (δ 4.80, d, $J = 5.2$ Hz) with the adjacent carbons firmly established the core part of the aglycon (Figure 1). However, the point of the attachment of the sugar, being either at C-4 or C-5, remained to be established. Information from a 2D phase-sensitive NOESY indicated an NOE interaction between the two aromatic protons (Figure 1), and this was further established by a difference NOE experiment where irridation of the proton at δ 7.36 (H-3) induced an NOE at δ 7.88 (7%, H-4), and *vice versa*. That the sugar was linked to an aromatic carbon C-5 was indicated from the HMBC correlation between the anomeric proton, δ 4.96 ppm, and the C-5 carbon at δ 149.3, the orientation of the glucose unit being β (δ 4.96, d, $J = 7.6$ Hz for the anomeric proton). From the above evidence, the structure of echinothiophene was established to be 5-*O*-β-D-glucopyranosyl-6-[(1*E*,3*E*)-6-hydroxy-1,3-hexadienyl]-2-hydroxymethyl-thieno[2,3-*e*]-isobenzofuran-8(6*H*)-one. To the best of our knowledge, echinothiophene is the first example of a natural product with such a carbon skeleton.

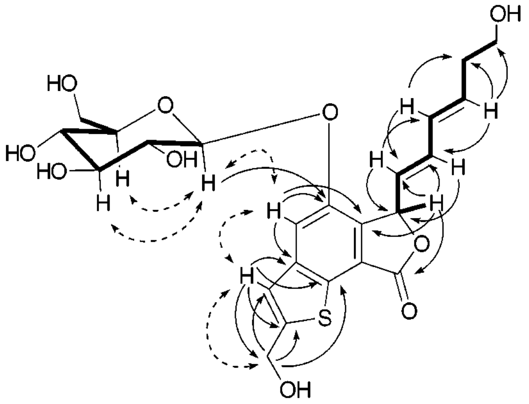

Figure 1. Connectivity established by COSY, HOHAHA, HSQC (bold lines), HMBC (arrows), and key NOE relationships (dashed arrows) from a phase-sensitive NOESY (the mixing time τ = 600 ms).

It is interesting to note that echinothiophene at equilibrium in MeOH solution exists as a mixture of epimers, **1** and **3**, that may arise *via* enol intermediate **2**. The pairs had almost identical UV spectra but displayed distinct HPLC retention times (ODS column, MeOH−H_2O 35:65) with a ratio of *ca.* 2 to 3. However, due to the rapid epimerization, we were unable to separate them. Fortunately, on crystallization from aqueous MeOH, the energetically more favorable isomer crystallized. Equilibration, however, was reestablished on dissolution as observed when procuring NMR data, the rate being slower in DMSO than in MeOH. After standing for a long time in DMSO as in the process of continuous NMR measurement, the proton spectrum of the diastereomerically pure echinothiophene changed into that of a mixture of the isomers. Molecular mechanics and dynamics calculations[9] indicated that epimer **1** (6*R*) is more stable than **2** (6*S*) (Δ −0.7 kcal/mol). Thus, it is believed that structure **1** is most probably the one that crystallized out and that for which NMR data were obtained.

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[9] Molecular mechanics and dynamics calculations were performed using Discover/INSIGHTII 97 (force field, CVFF) on a Silicon graphics O2 R1000 workstation (MSI).