Toddalosin, a New Biscoumarin, from *Toddalia asiatica* (L.) LAM. (*T. aculeata* PERS.)

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The X-ray structure of toddalosin (1), a new biscoumarin, isolated from *Toddalia asiatica* (L.) LAM. (*T. aculeata* PERS.) is described.

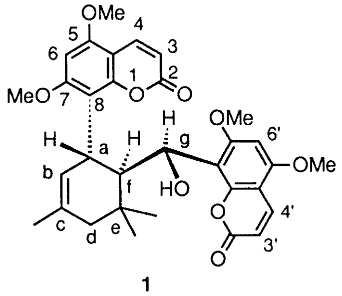
Keywords toddalosin; biscoumarin; X-ray analysis; structural establishment; *Toddalia asiatica* (*T. aculeata*); Rutaceae

In the previous paper[1] we briefly described the isolation of toddalosin (**1**), a new biscoumarin from *Toddalia asiatica* (L.) LAM. (*T. aculeata* PERS.). Now we present the details of its structure determination.

Toddalosin (**1**) was obtained as colorless prisms, mp 265—270 °C (benzene–ether), in a racemic form.[1] The molecular formula of $C_{32}H_{34}O_9$ was confirmed by elemental analysis and the desorption chemical ionization mass spectrum (D/CIMS) (MH^+ m/z: 563). The absorptions in the infrared (IR) ($CHCl_3$) at ν_{max} 1720 cm^{-1} and the ultraviolet (UV) (MeOH) spectra at λ_{max} 205 (log ε 4.78), 258 (4.14), and 327 (4.28) nm suggested the presence of not only a coumarin moiety in the molecule but also an 8-substituted 5,7-dimethoxycoumarin structure[2] based on the appearance of two methoxyl groups at δ 3.76 and 3.93, a pair of complementary doublets (J=9.5 Hz) at δ 5.74 and 7.56, and an aromatic proton at δ 6.06 as a singlet in the nuclear magnetic resonance (NMR) spectrum. This compound appeared to be a biscoumarin composed of 5,7-dimethoxycoumarin with a monoterpene unit interposed *via* the 8 position of a coumarin skeleton because of the observation of a repeated signal pattern [δ 3.79 and 4.03 (each 3H, s), 5.88 and 7.71 (each 1H, d, J=9.5 Hz), and 6.07 (1H, s)] in the NMR spectrum.

A secondary alcoholic function in the monoterpene unit was deduced from the observation of an IR absorption at 3500 cm^{-1} and an exchangeable 1H doublet (J=12.0 Hz) at δ 2.87 in the NMR spectrum. The double doublet signal (J=12.0 and 8.5 Hz) can be assigned to the carbinol proton (C_g-H) at the benzylic position from the chemical shift (δ 5.35). Two other methine signals attributable to C_f-H and C_a-H were observed at δ 3.13 as a double doublet (J=10.0 and 8.5 Hz) and δ 3.54 as a doublet (J=10.0 Hz), respectively. The partial structure of $C_aHC_fHC_gH$ deduced from the above assignments was futher confirmed by a decoupling experiment in the NMR spectrum. In addition, the NMR spectrum exhibited the presence of four signals attributable to a *gem*-dimethyl group (δ 1.14 and 1.35: C_e-Me_2), an olefinic methyl group (δ 1.59: C_c-Me), and an olefinic proton (δ 4.77: C_b-H) as singlets and that of a methylene signal as a geminally coupled doublets [δ 1.58 and 2.27 (each d, J=17.0 Hz): C_d-H_2], but these were not sufficiently informative to allow estimation of the structure. Therefore, the structure of **1** with relative stereochemistry was determined by X-ray crystallography.

A perspective drawing of **1** (Fig. 1) shows an overlapped conformation of two coumarin rings with *trans* configuration between the methine protons (C_a-H and C_f-H) on the cyclohexene ring in the monoterpene unit. In monomeric 5,7-dimethoxycoumarins the C_4 and C_6 proton signals normally appear in the range of δ 7.81—7.95 and 6.39—6.35, respectively, in the NMR spectra.[2] However, the corresponding signals in **1** were observed at higher field (C_4- and $C_{4'}$-H at δ 7.56 and 7.71; C_6- and $C_{6'}$-H at δ 6.06 and 6.07). This shielding could be reasonably explained by an overlapped structure of two coumarin rings in **1**. Though Kapil *et al.*[3] have applied the assignments for a monomeric coumarin to structural discussion of a biscoumarin, toddasin (**2**), our results indicate that simple application may lead to an incorrect conclusion.



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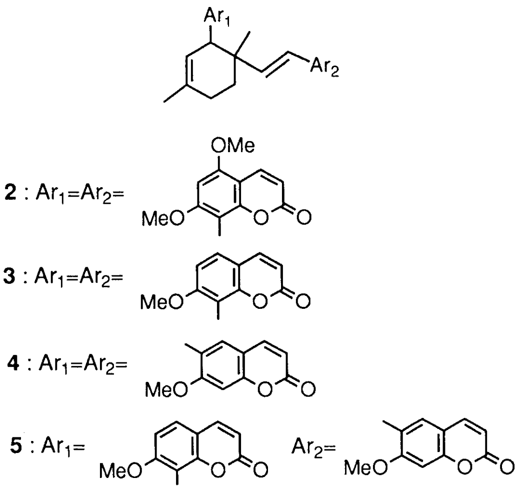

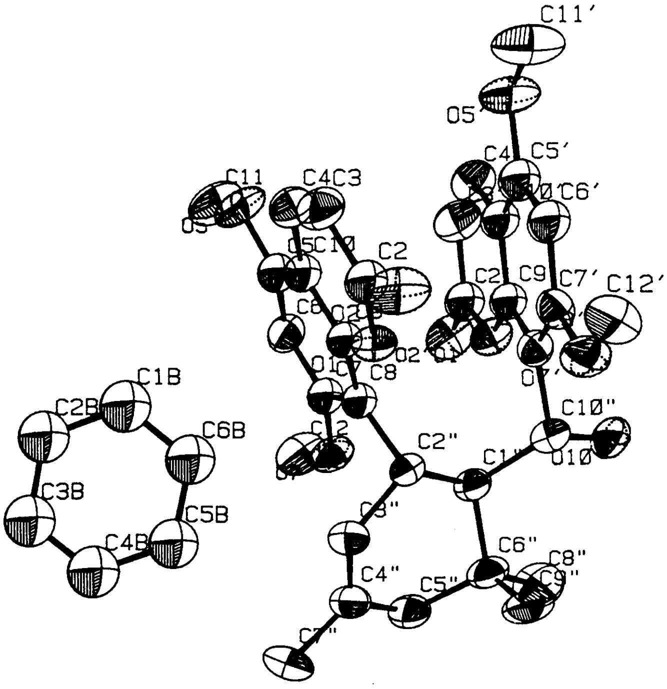

Fig. 1. ORTEP Drawing of 1

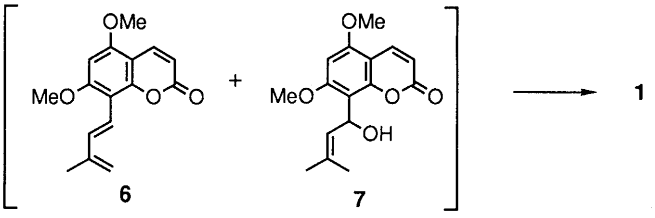

Chart 1

Four biscoumarins carrying a monoterpene unit [toddasin[3] (mexolide[4]) (**2**), phebalin[5] (**3**), thamnosin[6] (cyclobisuberodiene[7]) (**4**), and isothamnosin A[8] (**5**)] have been found in nature in racemic form. Toddasin (**2**) had been isolated from *T. asiatica*[3] and it was also isolated by us.[1] These biscoumarins have a 3-coumaryl-1,4-dimethyl-4-(β-coumarylvinyl)cyclohexene skeleton as a common monoterpene unit and would be synthesized biogenetically through [2+4] cycloaddition reaction between the side chains in 3-methyl-1,3-butadienylcoumarin derivatives [a diene (**6**)[9] in the case of formation of **2**]. On the other hand, toddalosin (**1**) contains a new type of 1,3,4,5,5-pentasubstituted cyclohexene ring in its molecule in place of the common 1,3,4,4-tetrasubstituted one in the known biscoumarins described above, and could be produced by a Diels–Alder type reaction, in which 5,7-dimethoxy-8-(3-methyl-1,3-butadienyl)coumarin (**6**) and 5,7-dimethoxy-8-(1-hydroxy-3-methyl-2-butenyl)coumarin (**7**) act as a diene and a dienophile, respectively, in the plant (Chart 1). A biomimetic synthesis of **1** is in progress.

Crystal Structure of 1 A colorless crystal from benzene was used for the structure determination. The cell dimensions and diffraction intensities were measured on a four-circle diffractometer (Rigaku, AFC-5), using graphite-monochromated MoK_α radiation.

Crystal Data: $C_{32}H_{34}O_9 \cdot C_6H_6$, monoclinic, space group $P2_1/c$, $a=14.009(2)$, $b=19.924(3)$, $c=11.916(2)$ Å, $\beta=98.23(1)°$, $V=3291.9(8)$ Å^3, $Z=4$, $D_{\text{calcd}}=1.29$ g/cm^3, $\mu=0.8$ cm^{-1}. Of the 6679 reflections measured with a $\omega<30<\omega-2\theta$ scan, 4281 were independently observed at the level of $F>3\sigma$ (F). The structure was solved by the direct method using the program MULTAN 74 and the atomic parameters were refined by the block-diagonal least-squares method. The final R factor was 0.096. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Analysis Center of Chiba University.

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References and Notes

1) H. Ishii, J.-I. Kobayashi, M. Ishikawa, J. Haginiwa, T. Ishikawa, *Yakugaku Zasshi*, **111**, 365 (1991); The experimental conditions and details of the spectral data are given here.
2) H. Ishii, J.-I. Kobayashi, T. Ishikawa, *Tetrahedron Lett.*, **32**, 6907 (1991); H. Ishii, J.-I. Kobayashi, H. Seki, T. Ishikawa, *Chem. Pharm. Bull.*, **40**, 1358 (1992).
3) P. N. Sharma, A. Shoeb, R. S. Kapil, S. P. Popli, *Phytochemistry*, **19**, 1258 (1980).
4) D. P. Chakraborty, S. Roy, A. Chakraborty, A. K. Mandal, B. K. Chowdhury, *Tetrahedron*, **36**, 3563 (1980).
5) K. L. Brown, A. I. R. Burfitt, R. C. Cambie, D. Hall, K. P. Mathai, *Aust. J. Chem.*, **28**, 1327 (1975).
6) J. P. Kutney, T. Inaba, D. L. Dreyer, *Tetrahedron*, **26**, 3171 (1970).
7) G. B. Guise, E. Ritchie, R. G. Senior, W. C. Taylor, *Aust. J. Chem.*, **20**, 2429 (1967).
8) A. G. Gonzalez, C. E. Diaz, H. D. Lopez, J. M. Dedina, L. F. Rodriguez, *An. Quim.*, **73**, 1501 (1977) [*Chem. Abstr.*, **88**, 133243*v* (1978)].
9) This coumarin was isolated from *Murraya gleinei* under the name of gleinadiene [V. Kumar, J. Reisch, D. B. M. Wickremaratne, R. A. Hussain, K. S. Adesina, S. Balasubramaniam, *Phytochemistry*, **26**, 511 (1987)].