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SB-204900, a Novel Oxirane Carboxamide from *Clausena lansium*

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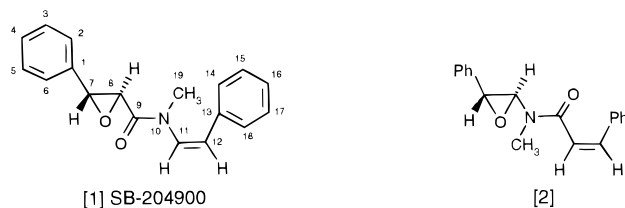
SB-204900 (**1**), a novel oxirane carboxamide, has been isolated from a hexane extract of the fruit tree *Clausena lansium* (Rutaceae). The structure of **1** was determined by detailed spectroscopic methods and unambiguously confirmed by a single-crystal X-ray diffraction study.

Clausena lansium is a fruit tree found in southern China and cultivated in Taiwan. In traditional medicine its leaves have been used for the treatment of coughs, asthma, and viral hepatitis as well as dermatological and gastrointestinal diseases.^{1–3} Previous studies^{3,4} have resulted in the isolation of the cinnamide derivatives lansamide I and lansiumamides A, B, and C, in addition to related pyrrolidinones.^{2,5–9} Our investigation of the hexane extract of the leaves from *C. lansium* (Lour.) Skeels (Rutaceae) has resulted in the isolation of a novel oxirane carboxamide, SB-204900 (**1**). We report here the structure determination of this novel compound.

Purification of the crude hexane extract was effected *via* sequential chromatography on Diaion HP20, HP20SS, and silica gel, followed by crystallization from ethyl acetate/hexane. In this way, SB-204900 (**1**) was isolated as colorless prisms.

The molecular formula was established as C₁₈H₁₇NO₂ by accurate mass measurement of the molecular ion at *m/z* 279 in the HREIMS and also by elemental analysis. The ¹H NMR spectrum showed a singlet methyl at 3.13 ppm, two finely coupled doublets at 3.77 and 3.80 ppm (*J* = 1.8 Hz), *cis*-coupled olefinic protons at 6.22 and 6.34 ppm (*J* = 8.6 Hz), and 10 aromatic protons of two monosubstituted benzene rings at 6.98–7.27 ppm. No exchangeable protons were observed in the ¹H NMR spectrum. The chemical shift of the singlet methyl (3.13 ppm) was consistent with an *N*-methylamide group, and a carbonyl resonance at 166.6 ppm in the ¹³C NMR spectrum supported this conclusion. This carbonyl group therefore accounted for one of the two oxygen atoms apparent from the molecular formula. On chemical shift grounds the remaining oxygen atom had to be associated with the protons resonating at 3.77 and 3.80 ppm and the corresponding carbon resonances at 56.9 and 57.9 ppm. This could only be accommodated by invoking an epoxy function; the 1.8 Hz coupling suggested a *trans*-disposition of the associated protons.^{10,11} Thus, the molecular formula could be accounted for by the presence of two phenyl groups, a *trans*-epoxide, an

N-methylamide, and a *cis*-olefin. The lack of coupling between the epoxy and olefinic protons, and the monosubstituted nature of the two phenyl groups, required the former groups to be separated by the *N*-methylamide function. Thus, only two structures, **1** and **2**, were possible. The former structure **1** was supported by a three-bond heteronuclear coupling observed in the COLOC spectrum from the olefinic carbon at 127.1 ppm to the NCH₃ at 3.13 ppm. However, the alternative structure **2** could not be entirely ruled out. The structure was firmly established as **1** by a single-crystal X-ray diffraction study, with suitable crystals obtained by slow crystallization from ethyl acetate/hexane. The crystal structure confirms the *trans*- stereochemistry about the oxirane ring and both the *cis* *N*-methylamide group and the *cis* double bond (1.320(8) Å) between atoms C11 and C12. The molecular structure of **1**



showing its relative stereochemistry is depicted in Figure 1, and the atomic coordinates for the non-hydrogen atoms are listed in Table 1. Full ¹H and ¹³C NMR assignments were obtained by ¹³C/¹H COSY and COLOC experiments and are presented in Table 2.

Experimental Section

Crystal Data: C₁₈H₁₇NO₂, *M* = 279.34, colorless prism, 0.45 × 0.10 × 0.10 mm, orthorhombic, space group *P*2₁2₁2₁, *T* = 223K, *a* = 7.066(3) Å, *b* = 7.486(8) Å, *c* = 28.25(1) Å, *V* = 1494.23(11) Å³, *D* = 1.242 g/cm³, *Z* = 4, *F*(000) = 592, *μ* = 0.755 cm⁻¹, *R* = 0.073, *R*_w = 0.079 for 991 unique reflections (*I* > 2σ(*I*)) in the range 2° < 2θ < 56°.

Data Collection and Structure Refinement. Data were collected on an Enraf-Nonius CAD-4 diffractometer

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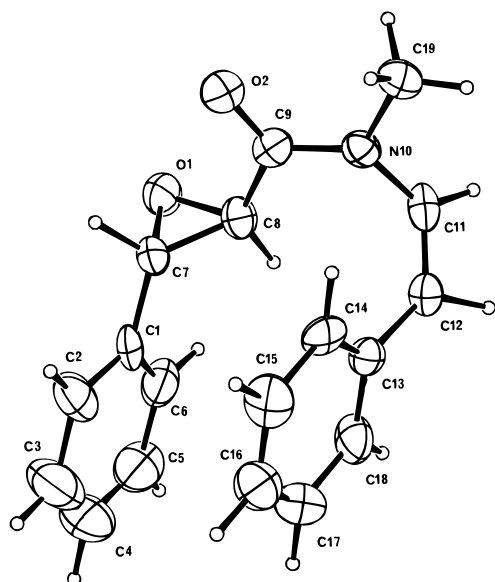


Figure 1. View of SB-204900 (**1**) from its crystal structure showing the relative stereochemistry. Non-hydrogen atoms are drawn as ellipsoids at the 50% probability level; hydrogen atoms are drawn as spheres of arbitrary size.

Table 1. Atomic Coordinates and Their Estimated Standard Deviations for SB-204900 (**1**)

atom	x	y	z	B ^a (Å ²)
O1	-0.1130(7)	0.3547(6)	0.1127(2)	3.7(1)
O2	0.0349(7)	0.3570(6)	0.0210(1)	3.7(1)
N10	-0.0318(7)	0.0642(7)	0.0103(2)	2.5(1)
C1	0.117(1)	0.2221(9)	0.1703(2)	3.2(1)
C2	0.299(1)	0.250(1)	0.1876(2)	4.2(2)
C3	0.344(1)	0.184(1)	0.2325(3)	6.5(2)
C4	0.215(2)	0.096(1)	0.2597(3)	6.7(3)
C5	0.033(2)	0.073(1)	0.2426(2)	5.5(2)
C6	-0.019(1)	0.136(1)	0.1982(2)	4.2(2)
C7	0.0733(9)	0.2898(9)	0.1213(2)	2.9(1)
C8	-0.0526(9)	0.1927(8)	0.0897(2)	2.9(1)
C9	-0.0143(9)	0.2135(9)	0.0374(2)	2.7(1)
C11	-0.099(1)	-0.1053(9)	0.0257(2)	2.8(1)
C12	-0.0219(9)	-0.2102(9)	0.0581(2)	2.7(1)
C13	0.1538(9)	-0.1836(8)	0.0859(2)	2.6(1)
C14	0.3097(9)	-0.0908(9)	0.0684(2)	3.0(1)
C15	0.475(1)	-0.076(1)	0.0958(3)	4.3(2)
C16	0.482(1)	-0.151(1)	0.1397(3)	4.9(2)
C17	0.329(1)	-0.243(1)	0.1574(3)	4.8(2)
C18	0.162(1)	-0.2580(9)	0.1304(2)	3.7(2)
C19	0.002(1)	0.079(1)	-0.0407(2)	3.7(2)

^a Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos \gamma)B(1,2) + ac(\cos \beta)B(1,3) + bc(\cos \alpha)B(2,3)]$.

equipped with graphite-monochromated molybdenum radiation using variable speed $\omega - 2\theta$ scans extended by 25% on each side for background measurements. Cell constants were derived from the setting angles of 25 reflections with $30^\circ < 2\theta < 35^\circ$, as measured on the diffractometer. The space group was assigned unambiguously from the systematic absences. A unique octant of 2150 data was collected. Three standard reflections measured every 3 h of X-ray exposure time showed a maximum decay of 1.4%; no correction was applied. Data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods using the SHELXS program¹² and refined by full-matrix least-squares procedures using the SDP software¹³ and neutral atom scattering factors. Non-hydrogen atoms

Table 2. ¹H- (400 MHz) and ¹³C-NMR (100 MHz) Data for SB-204900 (**1**) in CDCl₃

atom	δ_C	δ_H (multiplicity, coupling, Hz)	COLOC from C to:
1	135.5		H7, H3/5
2/6	125.8	6.98 (dd, 2.0, 7.4)	H3/5, H7
3/5	128.5	7.27 (m)	H2/6
4	128.2	7.25 (m)	
7	57.9	3.80 (d, 1.8)	H2/6
8	56.9	3.77 (d, 1.8)	
9	166.6		H11, H19
11	127.1	6.34 (d, 8.6)	H12, H19
12	127.7	6.22 (d, 8.6)	H14/18, H15/17
13	133.7		H11, H15/17, H16
14/18	128.4	7.18 (dd, 3.0, 6.7)	H12
15/17	128.5	7.23 (m)	
16	128.7	7.25 (m)	H15/17
19	34.6	3.13 (s)	

were refined with anisotropic displacement parameters. Many hydrogen atom positions were visible in successive difference Fourier maps, but hydrogens were assigned positions and isotropic thermal factors based on geometrical and crystallographic considerations and held fixed in the last refinement stages. An extinction correction refined in the later stages to a value of $6.05(1) \times 10^{-7}$. The refinement of 191 variables converged (max $\Delta/\sigma = 0.03$) to values of the standard crystallographic residuals listed above; the "goodness of fit" was 1.393. A final difference Fourier map showed maximum residuals of $\pm 0.326 \text{ e } \text{Å}^{-3}$.

General Experimental Procedures. Diaion HP 20 (styrene divinylbenzene cross-linked polymeric adsorbent) was supplied by Mitsubishi Chemical Industries Ltd., Tokyo, Japan. Silica gel (Kiesel gel 60, 230–400 mesh) was obtained from Merck (Art. No. 9385). EIMS was recorded on a VG Trio-2 single quadrupole mass spectrometer and HREIMS on a VG ZAB 1F double focusing mass spectrometer. UV and IR spectra were recorded on a Pye Unicam SP7-500 and Perkin-Elmer 1600 Series FTIR spectrophotometers, respectively. The ¹H and ¹³C NMR spectra were measured at 27 °C on a Bruker AM 400 spectrometer, equipped with a 5 mm ¹H/¹³C dual probe.

Plant Material. Fresh leaves of *C. lansium* were collected in the grounds of the Forest Research Institute of Malaysia (FRIM) in Kepong near Kuala Lumpur, Malaysia, on 3 May 1991. A voucher specimen is held at the FRIM. The milled dried leaves (7.8 kg) were divided into five parts and extracted in 10 L aspirators by soaking (24 h \times 3) in hexane. The combined extracts were concentrated using a Büchi vacuum rotary evaporator at 40–45 °C to afford 133 g of extract. The crude hexane extract (133 g) was dissolved in methanol:water (60:40) (1.5 L) and chromatographed on Diaion HP20 (7.5 \times 30 cm), eluting sequentially with methanol:water (60:40, 80:20, and 100:0) followed by acetone:water (60:40, 80:20, and 100:0). The 60% and 80% acetone eluates were combined, evaporated to dryness, and rechromatographed on Diaion HP20SS (4 \times 52 cm), eluting sequentially with methanol:water (80:20, 90:10, and 100:0). The 100% methanol eluate was evaporated to dryness to afford a yellow oil (12.7 g). This was further purified by chromatography on Si gel, eluting with hexane–ethyl acetate mixtures (6:1 grading to 4:1) to afford a white solid (7.34 g, 5.5%). Recrystallization from ethyl acetate–hexane gave colorless prisms.

SB-204900: (2*S,3*R**)-*N*-methyl-*N*-[(*Z*)-styryl]-3-phenyloxirane-2-carboxamide (1):** mp 59–60 °C; $[\alpha]_D^{25} + 14$ ($c = 1.0$, CHCl₃); UV (EtOH) λ max nm (ϵ) 261 (10 912); IR (KBr) ν max cm⁻¹ 3075, 3040, 1665, 1645, 1445, 1385, 1260; HREIMS m/z [M⁺] 279.1261 (calcd 279.1259 for C₁₈H₁₇NO₂); EIMS m/z (rel int) [M⁺] 279 (14), 250 (4), 220 (19), 193 (25), 173 (43), 144 (68), 133 (69), 117 (47), 99 (55), 91 (100), 77 (35), 65 (29); ¹H and ¹³C NMR see Table 2. Anal. Calcd for C₁₈H₁₇NO₂: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.31; H, 6.03; N, 5.11.

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Supporting Information Available: X-ray crystallographic data for **1** (12 pages). Ordering information is given on any current masthead page. Atomic coordinates including tables of bond distances and angles from the X-ray results have also been deposited with the Cambridge Crystallographic Data Centre.

References and Notes

- (1) Kan, W. S. In *Manual of Medicinal Plants in Taiwan*; The Chinese Medical Publishing: Taiwan, 1967; Vol. 2, p 372.
- (2) Yang, M. H.; Chen, Y. Y.; Huang, L. *Phytochemistry* **1988**, *27*, 445–450.
- (3) Lin, J.-H. *Phytochemistry* **1989**, *28*, 621–622.
- (4) Prakash, D.; Raj, K.; Kapil, R. S.; Popli, S. P. *Ind. J. Chem. Sect. B* **1980**, *19B*, 1075–1076.
- (5) Chen, Y. R.; Yang, M. H.; Huang, L.; Liu, G. T.; Benz, U. (Chinese Academy of Medical Sciences; Bayer, A. G.) German Patent DE 3 431 257, 20 Mar 1986; *Chem. Abstr.* **1986**, *105*, 72689r.
- (6) Yang, M.; Cao, Y.; Li, W.; Yang, Y.; Cheng, Y.; Huang, L. *Yaouxue Xuebao*, **1987**, *22*, 33–40; *Chem. Abstr.* **1987**, *106*, 153109z.
- (7) Lakshmi, V.; Raj, K.; Kapil, R. S.; Patnaik, G. K. *Indian Drugs* **1988**, *26*, 105–106.
- (8) Yang, M.; Chen, Y.; Huang, L. *Huaxue Xuebao*, **1987**, *45*, 1170–1174; *Chem. Abstr.* **1988**, *108*, 218952g.
- (9) Cheng, J.; Yang, J.; He, C.; Zheng, Q. *Chin. Sci. Bull.* **1989**, *34*, 957–959.
- (10) Wahlberg, I.; Eklund, A.-M.; Nordfors, K.; Vogt, C.; Enzell, C. R.; Berg, J.-E. *Acta Chem. Scand. Ser. B* **1988**, *42*, 708–716.
- (11) Morisaki, N.; Funabashi, H.; Furukawa, J.; Shimazawa, R.; Kanematsu, A.; Ando, T.; Okuda, S.; Iwasaki, S. *Chem. Pharm. Bull.* **1992**, *40*, 2945–2953.
- (12) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: England, 1985; pp 175–189.
- (13) Enraf Nonius Structure Determination Package; Enraf Nonius: Delft, The Netherlands, 1979.

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