

## SPECTROSCOPIC STUDIES OF BRUSATOL

YOSHIHIRO HARIGAYA,\* YAEKO KONDA, MIEKO IGUCHI, MASAYUKI ONDA,

*School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan*

XIAN LI,\* LIJUN WU, SHAOSHUN LI, and XUELONG SUN

*Shenyang College of Pharmacy, Wenhua-lu, Shenyang, China*

ABSTRACT.—The absolute stereochemistry of brusatol has been confirmed to be 5*S*, 7*R*, 8*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*S*, 14*S*, 15*R* by a combination of 2D nmr [ $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  (one-bond and long-range) COSY], nOe, and cd spectroscopic analyses.

In our studies on biologically active natural products, an antitumor quassinoid, brusatol [**1**], was recently isolated from the traditional Chinese medicine "Yandanzi," *Brucea javanica* (L.) Merr (Simaroubaceae) (1). Sim *et al.* (2) had previously reported that **1** was a bitter principle of *Brucea sumatrana* and that 2',3'-dihydrobrusatol, which was obtained by the hydrogenation of **1**, was identical with bruceine A [**2**]. It is known that bruceines A [**2**], B [**3**], and C [**4**], bruceantarin [**5**], bruceantin [**6**], and bruceantiol [**7**] are the C<sub>20</sub> quassinoids with the same basic skeleton as that of **1** and only differ in the nature of 15-ester grouping (3-7). The absolute stereochemistry of bruceine C [**4**] was elucidated on the basis of X-ray analysis of its tetraacetate by Polonsky *et al.* (7). Thus, the absolute stereochemistry of the basic skeleton of these quassinoids was assumed to be the same as that of **4**. This paper is concerned with an approach to the absolute stereochemistry of **1** by a combination of high-resolution ( $^1\text{H}$ , 400 MHz;  $^{13}\text{C}$ , 100.6 MHz) nmr and cd spectroscopic analyses.

## RESULTS AND DISCUSSION

NMR SPECTROSCOPY.—The nmr spectra were taken in pyridine-*d*<sub>5</sub> unless otherwise cited. Because the resonances of H-15 and C-14 were obscured at ambient temperature and those of H-5, H-14, C-5, and C-15 were slightly broad, the spectra were measured at 50°.

The 1D nmr spectra showed the number of hydrogens (except three hydroxyls) and carbons corresponding to the molecular formula C<sub>26</sub>H<sub>32</sub>O<sub>11</sub> of **1**. The number of hydrogens attached to each individual carbon was determined by DEPT experiments: five methyls, three methylenes, eight methines, and ten quaternary carbons. Hydroxyls (exchangeable with D<sub>2</sub>O) were examined in DMSO-*d*<sub>6</sub>. Several protons (H-1 $\alpha$  and H-9, H-7 and H<sub>B</sub>-20, H-14 and H<sub>A</sub>-20) that displayed close or overlapping resonances in pyridine-*d*<sub>5</sub> showed more separated resonances for each pair in DMSO-*d*<sub>6</sub>.

The  $^1\text{H}$ - $^1\text{H}$ , one-bond  $^1\text{H}$ - $^{13}\text{C}$ , and long-range  $^1\text{H}$ - $^{13}\text{C}$  COSY spectra are shown in Figures 1-3, respectively, and the spectral parameters including  $^1\text{H}$ - $^1\text{H}$  coupling constants are given in Table 1. The 2D nmr spectra of **1** are published by us for the first time. The assignments of ring protons (in part) for **1** (2), **2** (5), **3** (5,6), and **6** (7) were made on the basis of the comparison with those for related quassinoids and the application of the empirical rules. The assignments of carbons for **3** (8), **4** (8), and **6** (9) have been previously reported, but it was found that there are large discrepancies in the carbon resonances at C-8 (-3.1 ppm), C-9 (2.5 ppm), C-10 (5.8 ppm), and C-15 (2.8 ppm) between ours and those cited above.

Each proton and carbon belonging to protonated carbons was readily associated with each other by the  $^1\text{H}$ - $^{13}\text{C}$  (one-bond) COSY spectrum. Therefore, the assignments of these carbons were straightforward from the proton assignments which were achieved as follows.

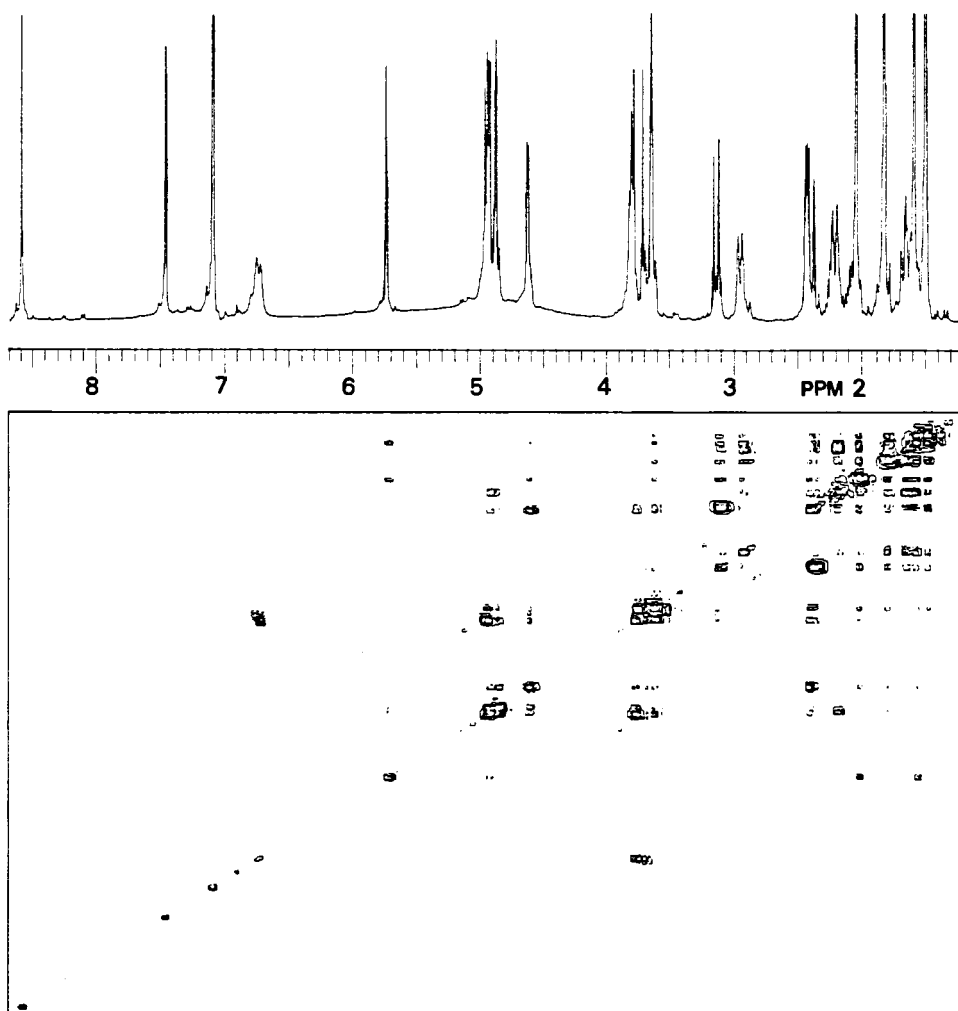


FIGURE 1.  $^1\text{H}$ - $^1\text{H}$  COSY spectrum of brusatol [1].

Three methyls (vinylic) were easily distinguished. A coupling was observed between  $\text{H}_3$ -19 and H-5 by decoupling experiments. The correlation of  $\text{H}_3$ -4' and  $\text{H}_3$ -5' with H-2' (vinylic), which was assigned on the basis of its proton and carbon chemical shifts, was shown by the  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  (long-range) COSY spectra. These two methyls were differentiated by nOe experiments:  $\text{H}-2' \longleftrightarrow \text{Me}-4'$ . The distinction between two methyls,  $\text{H}_3$ -18 (angular) and  $\text{H}_3$ -23 (OMe), was straightforward on the basis of their proton and carbon chemical shifts. Decoupling experiments showed that one methylene,  $\text{H}_2$ -6, constitutes the spin system,  $\text{H}-5-\text{H}_2-6-\text{H}-7$ , including H-5 coupled to  $\text{H}_3$ -19. Two methylenes,  $\text{H}_2$ -1 and  $\text{H}_2$ -20, were readily identified by the observation of correlation of H-1 $\alpha$  and  $\text{H}_A$ -20 with  $\text{H}_3$ -18 and H-9, respectively ( $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$ ). Decoupling experiments indicated that H-11 containing a geminal hydroxyl is vicinally coupled to H-9 (decoupling) which is correlated to  $\text{H}_A$ -20 ( $^1\text{H}$ - $^1\text{H}$ ) and  $\text{H}_2$ -1, H-7,  $\text{H}_3$ -18, and  $\text{H}_B$ -20 ( $^1\text{H}$ - $^{13}\text{C}$ ). Two methines with oxygen groupings, H-12 and H-15, were unambiguously assigned: H-12 was related to H-11 ( $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$ ) and H-14 ( $^1\text{H}$ - $^{13}\text{C}$ ); H-15 was vicinally coupled to H-14 (decoupling). The assignments of three hydroxyls were readily made by the  $^1\text{H}$ - $^1\text{H}$  COSY spectrum

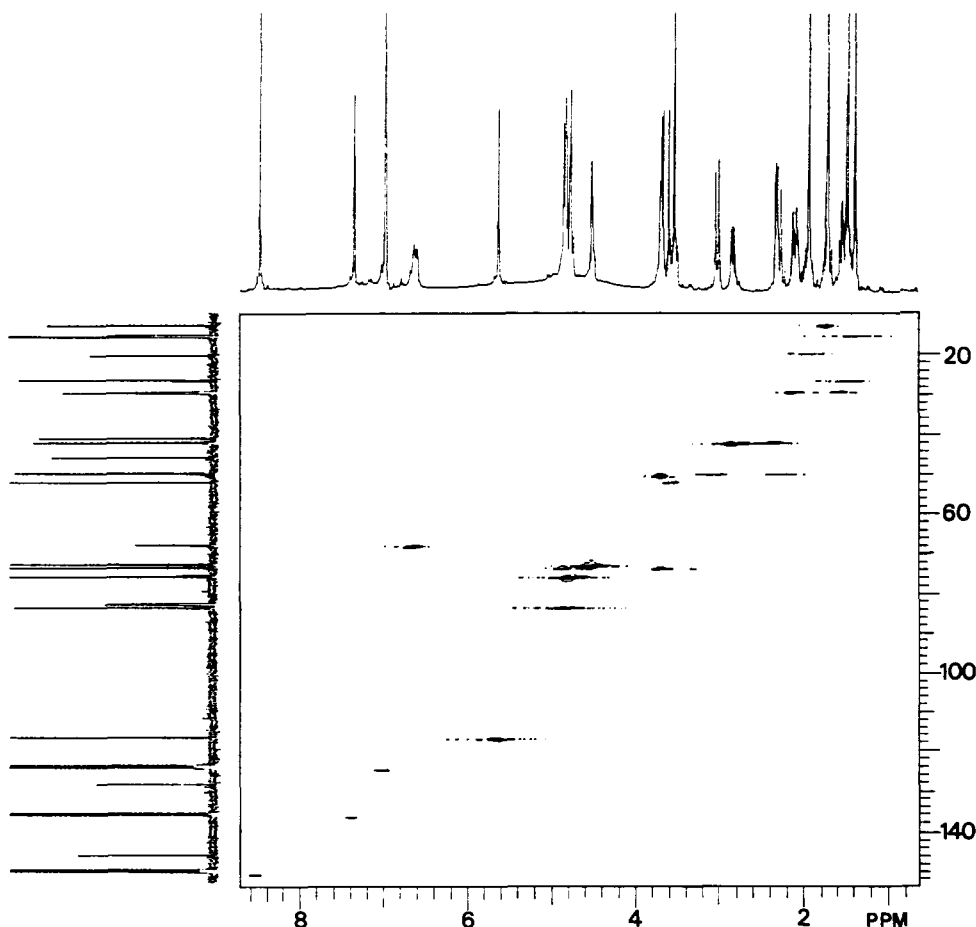


FIGURE 2.  $^1\text{H}$ - $^{13}\text{C}$  (one-bond) COSY spectrum of brusatol [1].

taken in  $\text{DMSO}-d_6$ . Quaternary carbons were completely assigned by the  $^1\text{H}$ - $^{13}\text{C}$  (long-range) COSY spectrum as well as their chemical shifts.

The relative stereochemistry and ring conformation were established by nOe (Table 2) and decoupling experiments. 13,20-Epoxy grouping sterically required  $8\beta$  (ax)-C-20 and  $13\beta$  (ax)-O-21 [ $13\alpha$  (eq)-COOMe]<sup>1</sup> with respect to C ring regardless of its conformation. Irradiation of H-9 ( $\text{DMSO}-d_6$ ) gave nOe's at 12-OH and H-15, leading to H-9 $\alpha$  (ax), 12 $\alpha$  (ax)-OH [H-12 $\beta$  (eq)] and 14 $\alpha$  (ax)-C-15 [H-14 $\beta$  (eq)] with respect to C ring with a chair form. As a result, the B/C trans and C/D cis ring junctures were established as shown in structural fragment A. An nOe observed between H-9 $\alpha$  and H-11 and a coupling constant,  $J_{9,11} = 4.5$  Hz, suggested H-11 $\alpha$  (eq) and 11 $\beta$  (ax)-OH. The lack of a coupling constant between H-11 $\alpha$  and H-12 $\beta$  (dihedral angle ca.  $90^\circ$ ) suggested the slight deformation of C ring to relieve the strain caused by two  $\alpha$  (axial) and three  $\beta$  (axial) substituents.

NOe's observed between H-6 ( $\delta$  1.652) and H<sub>3</sub>-18 and between H<sub>3</sub>-18 and H<sub>B</sub>-20 ( $\delta$  4.955) led to H-6 $\beta$  (ax) ( $\delta$  1.652),  $8\beta$  (ax)-C-20, and 10 $\beta$  (ax)-Me-18 with respect to B ring with a chair form. An nOe observed between H-7 and H<sub>A</sub>-20 ( $\text{DMSO}-d_6$ ) and

<sup>1</sup> $\alpha$  and  $\beta$  notations are tentatively used until the absolute stereochemistry is made clear.

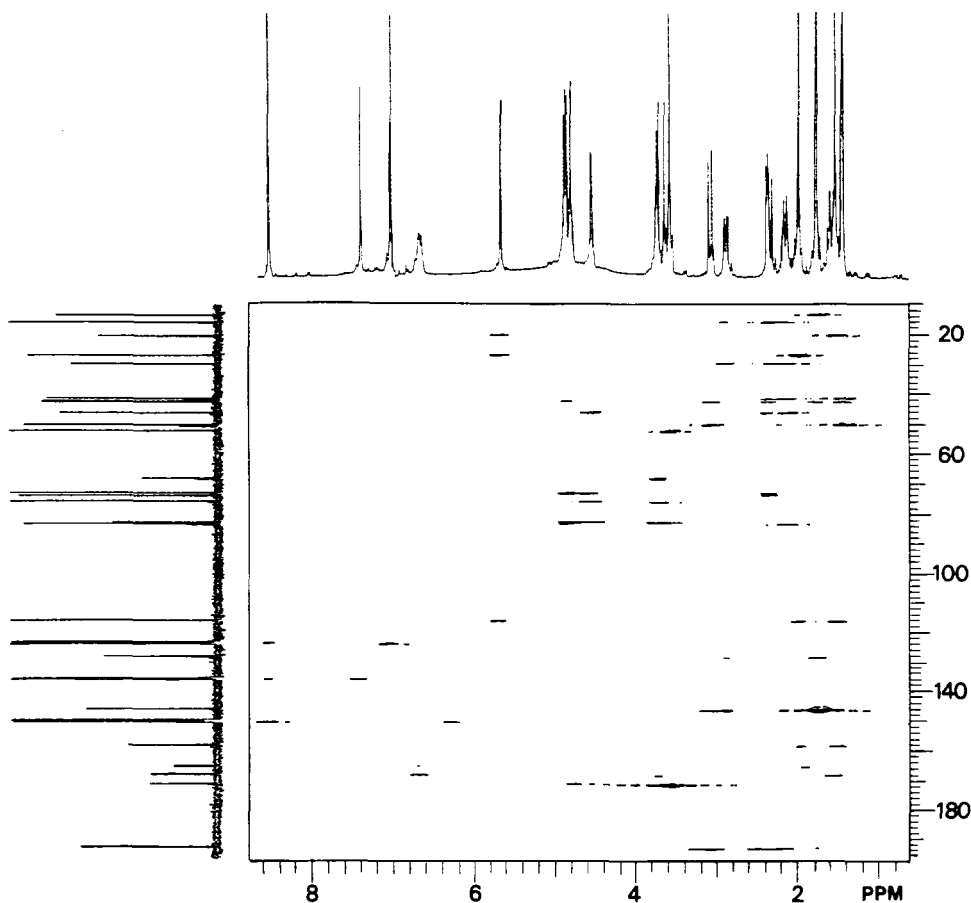


FIGURE 3.  $^1\text{H}$ - $^{13}\text{C}$  (long-range) COSY spectrum of brusatol [1].

coupling constants  $J_{6\alpha,7} = J_{6\beta,7} = 2.5$  Hz suggested H-7 $\beta$  (eq) with respect to B ring and the B/D cis ring juncture. Saturation of H-5 afforded nOe's at H-1 ( $\delta$  2.395) and H-9 $\alpha$ , leading to H-1 $\alpha$  (ax) ( $\delta$  2.395), H-5 $\alpha$  (ax), and H-9 $\alpha$  (ax) with respect to A ring and/or B ring and the A/B trans juncture. A coupling constant,  $J_{5,6\beta} = 13.0$  Hz, was in accord with H-5 $\alpha$  (ax). At this stage, the A ring conformation cannot be distinguished among an envelope, a half-boat, and a half-chair form.

It is known that  $\delta$  lactones adopt a half-chair or a half-boat form with a planar C(=O)-O-C grouping (10). A Dreiding model showed that a half-boat form of the D ring remarkably lengthens the distance between C-20 and O-21, and as a result, the formation of an ether bridge between C-13 and C-20 sterically becomes impossible. Thus, it was considered that the D ring adopts a strain-free half-chair form. NOe's observed among H-9 $\alpha$ , 12 $\alpha$ -OH, and H-15 and a coupling constant,  $J_{14,15} = 13.0$  Hz, led to H-15 $\alpha$  (ax) and 15 $\beta$  (eq)-*O*-seneciate with respect to the D ring. Further evidence supporting the B/D and C/D cis ring junctures was obtained by the observation of nOe's at H-14 $\beta$  and H<sub>A</sub>-20 on saturation of H-7 $\beta$  (DMSO-*d*<sub>6</sub>).

The Dreiding model **1a**<sup>2</sup> based on the data above clearly accounts for the additional data presented in Tables 1 and 2.

<sup>2</sup>An A ring is shown in an envelope form for convenience.

TABLE 1. Nmr Data for Brusatol [1].<sup>a</sup>

Carbon	$\delta_c$	Correlated proton <sup>b</sup>		<sup>1</sup> H- <sup>1</sup> H <sup>c</sup>
		One-bond <sup>d</sup>	Long-range	
C-1 . . . . .	50.252 t	H-1 $\alpha$ 2.395 d (2.589 d) H-1 $\beta$ 3.135 d	H-5, H-6 $\beta$ , H <sub>3</sub> -18	H-1 $\beta$ , H <sub>3</sub> -18  H-1 $\alpha$
C-2 . . . . .	193.050 s		H-1 $\alpha$ , H-1 $\beta$	
C-3 . . . . .	146.062 s		H-1 $\beta$ , H-5, H <sub>3</sub> -19	
C-4 . . . . .	128.324 s		H-5, H <sub>3</sub> -19	
C-5 . . . . .	42.667 d	H-5 2.950 br d (2.902 d)	H <sub>3</sub> -19	H-6 $\alpha$ , H-6 $\beta$ , H <sub>3</sub> -19
C-6 . . . . .	29.812 t	H-6 $\alpha$ 2.208 dt H-6 $\beta$ 1.652 ddd	H-5	H-5, H-6 $\beta$ , H-7 H-5, H-6 $\alpha$
C-7 . . . . .	83.673 d	H-7 4.933 t (4.915 t)	H-6 $\alpha$ , H-9	H-6 $\alpha$ , H-9
C-8 . . . . .	41.587 s		H-1 $\alpha$ , H-1 $\beta$ , H-6 $\alpha$ H-6 $\beta$ , H-9, H <sub>3</sub> -18	
C-9 . . . . .	42.426 d	H-9 2.432 d (2.147 d)	H-1 $\alpha$ , H-1 $\beta$ , H-7, H <sub>3</sub> -18, H <sub>B</sub> -20	H-11, H <sub>A</sub> -20
C-10 . . . . .	46.351 s		H-6 $\alpha$ , H-11, H-12	
C-11 . . . . .	73.237 d	H-11 4.626 d (4.004 t)	H-9, H-12	H-9, H-12 (11-OH)
C-12 . . . . .	76.150 d	H-12 4.879 s (4.109 d)	H-11, H-14	H-11, (12-OH)
C-13 . . . . .	82.928 s		H-11, H-12, H-14	
C-14 . . . . .	50.805 s	H-14 3.800 d (3.265 d)		H-15
C-15 . . . . .	68.328 d	H-15 6.737 d (5.920 d)	H-14	H-14
C-16 . . . . .	168.265 s		H-6 $\beta$ , H-15	
C-18 . . . . .	15.912 q	H <sub>3</sub> -18 1.503 s	H-1 $\alpha$ , H-5	H-1 $\alpha$
C-19 . . . . .	13.429 q	H <sub>3</sub> -19 1.825 d		H-5
C-20 . . . . .	73.926 t	H <sub>A</sub> -20 3.793 d (3.613 d) H <sub>B</sub> -20 4.955 d (4.517 d)	H-9	H-9, H <sub>B</sub> -20  H <sub>A</sub> -20
C-22 . . . . .	171.461 t		H-12, H <sub>3</sub> -23	
C-23 . . . . .	52.422 q	H <sub>3</sub> -23 3.646 s		
C-1' . . . . .	165.443 s		H-15, H <sub>3</sub> -5'	
C-2' . . . . .	116.189 d	H-2' 5.738 s	H <sub>3</sub> -4', H <sub>3</sub> -5'	H <sub>3</sub> -4', H <sub>3</sub> -5'
C-3' . . . . .	158.312 s		H <sub>3</sub> -4', H <sub>3</sub> -5'	

TABLE 1. Continued.

Carbon	$\delta_c$	Correlated proton <sup>b</sup>		<sup>1</sup> H- <sup>1</sup> H <sup>c</sup>
		One-bond <sup>d</sup>	Long-range	
C-4' . . . . .	20.354 q	H <sub>3</sub> -4' 1.590 s	H-2', H <sub>3</sub> -5'	H-2' (H <sub>3</sub> -5')
C-5' . . . . .	27.101 q	H <sub>3</sub> -5' 2.042 s 3-OH (7.822 s) 11-OH (4.723 d) 12-OH (5.425 d)	H-2', H <sub>3</sub> -4'	H-2' (H <sub>3</sub> -4') (H-1 $\alpha$ , H-1 $\beta$ , H <sub>3</sub> -19) (H-11) (H-12)

<sup>a</sup>The spectra were taken on a Varian XL-400 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100.6 MHz) in pyridine-*d*<sub>5</sub>; ppm.

<sup>b</sup>These data were obtained by <sup>1</sup>H-<sup>13</sup>C COSY experiments.

<sup>c</sup>These data were obtained by <sup>1</sup>H-<sup>1</sup>H COSY experiments; the data in parentheses were additionally obtained in DMSO-*d*<sub>6</sub>.

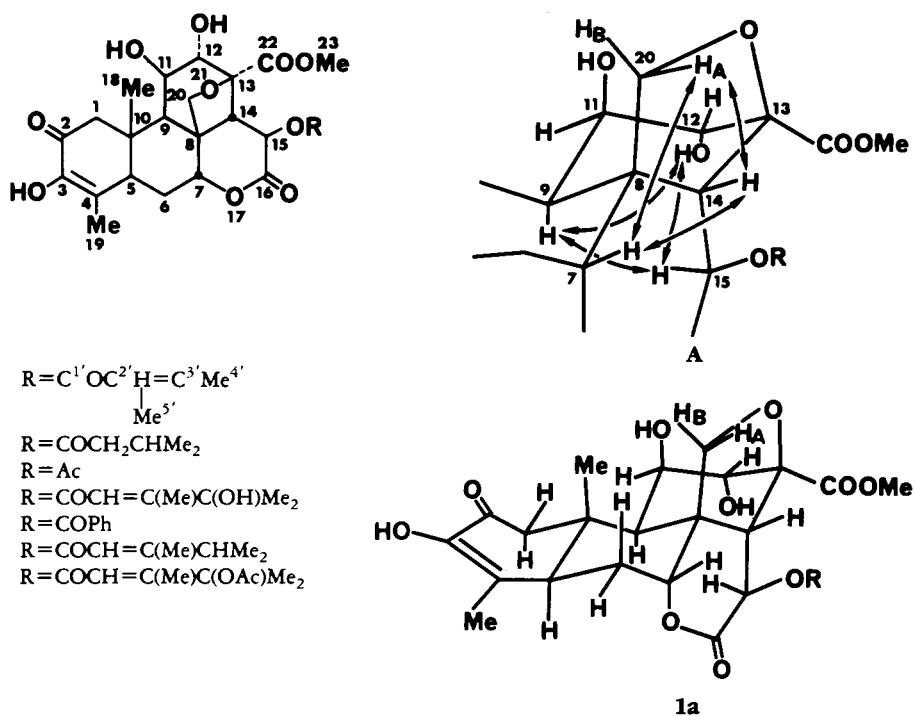
<sup>d</sup>The data in parentheses were obtained in DMSO-*d*<sub>6</sub>. Coupling constants (Hz) were as follows:  $J_{1\alpha,\beta} = 16.0$ ,  $J_{5,6\alpha} = 2.5$ ,  $J_{5,6\beta} = 13.0$ ,  $J_{5,19} = 1.3$ ,  $J_{6\alpha,\beta} = 14.5$ ,  $J_{6\alpha,7} = J_{6\beta,7} = 2.5$ ,  $J_{9,11} = 4.0$ ,  $J_{14,15} = 13.0$ ,  $J_{20A,B} = 7.3$ , ( $J_{11,11-OH} = J_{12,12-OH} = 4.7$ ).

CD SPECTROSCOPY.—The absolute stereochemistry was examined by means of cd spectroscopy. It is well known that the cd spectra of  $\alpha,\beta$ -unsaturated ketones show the characteristic  $n \rightarrow \pi^*$  Cotton effects, the sign of which is due to the ring conformations containing a C=C=O grouping (11). A number of  $\Delta^1$ -3-oxo-5 $\alpha$ -steroids with the A/B trans ring juncture, in which the A ring adopted an envelope or a half-boat form, indicated negative  $n \rightarrow \pi^*$  Cotton effect (11–13). Sznarcke (11, 14) pictorially correlated the sign of the  $n \rightarrow \pi^*$  Cotton effect with the A-ring conformations as shown in Figure 4. The C-4–C-5 bond in the right lower back octant of an envelope form and the C-1–C-2 bond in the left upper one of a half-boat form afford a negative contribution to the  $n \rightarrow \pi^*$  Cotton effect. The cd spectrum of **1** indicated a Cotton effect  $[\theta]_{312.5} - 15340$

TABLE 2. NOe Data for Brusatol [**1**].

Irradiated Proton	Observed Proton (nOe %)
H-1 $\alpha$ . . . . .	H-1 $\beta$ (10.3%)
H-5 . . . . .	H-1 $\alpha$ (2.9%), H-6 $\alpha$ (2.3%), H-9 (2.9%)
H-6 $\beta$ . . . . .	H-6 $\alpha$ (8.0%), H-7 (2.9%), H <sub>3</sub> -18 (1.2%)
H-7 <sup>a</sup> . . . . .	H-14 (6.3%), H <sub>A</sub> -20 (2.5%)
H-9 . . . . .	H-15 (13.9%)
H-9 <sup>a</sup> . . . . .	H-5 (10.4%), H-11 (4.2%), 12-OH (1.0%), H-15 (8.3%)
H-11 . . . . .	H-1 $\alpha$ (4.0%), H-1 $\beta$ (7.2%), H-9 (4.0%), H-12 (8.0%)
12-OH <sup>a</sup> . . . . .	H-11 (2.1%), H-12 (8.0%)
H-14 <sup>a</sup> . . . . .	H-7 (4.2%), H-12 (4.2%)
H-15 . . . . .	H-9 (8.0%)
H-15 <sup>a</sup> . . . . .	12-OH (1.0%)
H <sub>3</sub> -18 . . . . .	H-1 $\beta$ (2.9%), H <sub>B</sub> -20 (7.6%)
H <sub>A</sub> -20 . . . . .	H <sub>B</sub> -20 (10.0%)
H <sub>A</sub> -20 <sup>a</sup> . . . . .	H-7 (4.3%), H <sub>B</sub> -20 (11.0%)
H-2' . . . . .	H-12 (2.9%), H <sub>3</sub> -4' (2.4%)
H <sub>3</sub> -4' . . . . .	H-2' (11.4%), H <sub>3</sub> -5' (2.4%)
H <sub>3</sub> -5' . . . . .	H <sub>3</sub> -4' (2.9%)

<sup>a</sup>These data were obtained in DMSO-*d*<sub>6</sub>.



SCHEME 1

(Figure 5). The inspection of the molecular drawing based on X-ray analysis by Polonsky *et al.* (7) suggested that the A ring in bruceine C [4] tetraacetate adopts an envelope form with a planar diosphenol grouping. If it is assumed that the A ring in **1** adopts an envelope form in solution, the observed negative  $n \rightarrow \pi^*$  Cotton effect is explainable by Figure 4a. Thus, the  $5S, 10S$  configuration was assigned to **1**. It seems probable that this assignment is supported by the cd spectrum of 3,4-dihydrobruceine B, which shows a positive  $n \rightarrow \pi^*$  Cotton effect (4). The absolute configurations at the remaining asymmetric centers were assigned as  $7R, 8R, 9R, 11R, 12S, 13S, 14S, 15R$  on the basis of the relative stereochemistry. The absolute stereochemistry of **1** obtained above was in accord with that of **4**.

## EXPERIMENTAL

GENERAL.—Melting points were determined on a micro hot-stage apparatus and are uncorrected. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: uv, Hitachi EPS-2U; cd, JASCO J-20; ir, Hitachi 260-30;  $^1H$  nmr, XL-400 at 400 MHz;

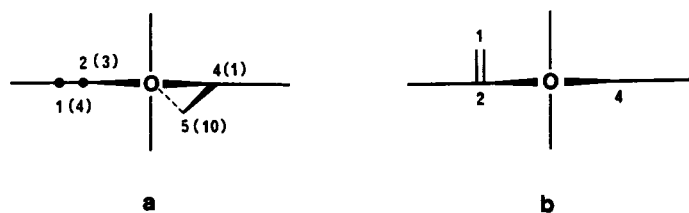


FIGURE 4. Negative  $n \rightarrow \pi^*$  Cotton effect and A-ring conformation in  $\Delta^1$ -3-oxo-5 $\alpha$ -steroids (A/B trans) and brusatol [**1**]: a, Envelope form; b, Half-boat form. Figures in parentheses are the numbering for **1**.

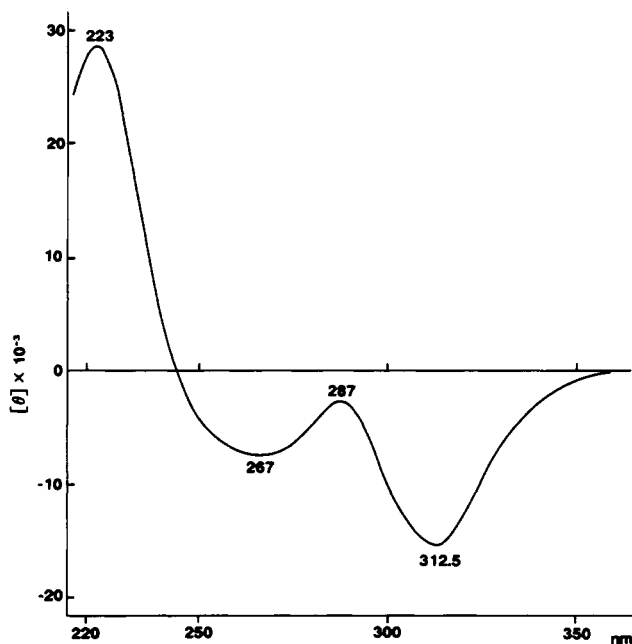


FIGURE 5. Cd spectrum of brusatol [1].

$^{13}\text{C}$  nmr, Varian XL-400 at 100.6 MHz; hrms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B.

All nmr spectra were taken at a probe temperature of  $50^\circ$  using a 5-mm tube.

$^1\text{H}$ - $^1\text{H}$  COSY:  $^1\text{H}$  single probe; relaxation delay 1 sec;  $90^\circ$  ( $^1\text{H}$ ) = 15  $\mu\text{sec}$ ;  $90^\circ$  mixing pulse;  $F_1 = F_2 = 3238$  (2891 in  $\text{DMSO}-d_6$ ) Hz; data matrix  $1024 \times 128$ ; 16 scans during 128 time increments (zero filling in  $F_1$ ); 2 dummy scans; spectra were symmetrized about diagonal axis using FOLDT command after 20 transformations.

$^1\text{H}$ - $^{13}\text{C}$  COSY:  $^{13}\text{C}$ , 30–105 MHz probe; relaxation delay 1 sec; 1 dummy scan;  $90^\circ$   $^1\text{H}$  and  $^{13}\text{C}$  pulses were calibrated at 31.0 and 9.7  $\mu\text{sec}$ , respectively. One-bond correlation:  $F_1 = 3243$  Hz,  $F_2 = 14389$  Hz; data matrix  $2048 \times 512$ ; 96 scans during 64 time increments; acquisition time 0.071 sec;  $^1J_{\text{CH}}$  (average) 140 Hz; size of final data points 2K. Long-range correlation:  $F_1 = 3257$  Hz,  $F_2 = 18904$  Hz; data matrix  $2048 \times 512$ ; 1408 scans during 96 time increments (zero filling in  $F_1$ ); acquisition time, 0.054 sec;  $^{\text{LR}}J_{\text{CH}}$  (average) 7.0 Hz; size of final data points 2K.

The nOe spectra were recorded by means of nOe difference spectroscopy. The pre-irradiation time of each resonance was 2 sec. The interpulse delay was 0 sec. The irradiation data sets were interleaved to cancel drift and changing magnet homogeneity. These spectra were transformed by the difference between two free induction decays.

**BRUSATOL [1].**—Extraction and isolation of **1** from *B. javanica* have been described by Li *et al.* (1). Colorless prisms, mp  $274$ – $276^\circ$  ( $\text{Me}_2\text{CO}$ ) [lit. (2) mp  $276$ – $278^\circ$  ( $\text{Me}_2\text{CO}$ )];  $R_f$  0.39 [Si gel,  $\text{CHCl}_3$ - $\text{MeOH}$ , (10:1)];  $[\alpha]^{20}_{\text{D}} + 39.1^\circ$  ( $c = 1.50$ ,  $\text{Me}_2\text{CO}$ ) [lit. (2)  $[\alpha]^{26}_{\text{D}} + 43.6^\circ$  ( $c = 1.50$ ,  $\text{Me}_2\text{CO}$ )]; uv  $\lambda$  max ( $\text{MeOH}$ ) ( $\log \epsilon$ ) 331 (2.89), 275 (4.11), 217 (4.39); cd ( $c = 4.0 \times 10^{-5}$ ,  $\text{MeOH}$ )  $[\theta]^{25}$  (nm) 0 (360),  $-15340$  (312.5) (negative maximum),  $-2600$  (287.0) (positive maximum),  $-7540$  (267.0) (negative maximum), 0 (244.0),  $+28600$  (223.0) (positive maximum); ir  $\nu$  max ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$  1751, 1731, 1672, 1646; hrms  $m/z$   $[\text{M}]^+$  520.1930 (520.1944 for  $\text{C}_{26}\text{H}_{32}\text{O}_{11}$ ). Anal. calcd for  $\text{C}_{26}\text{H}_{32}\text{O}_{11} \cdot \frac{1}{4}\text{H}_2\text{O}$ , C 59.48, H 6.24; found C 59.54, H 6.29.

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