ABSOLUTE STRUCTURE OF BRUCEINE H BY X-RAY ANALYSIS

Yaeko Konda,*[a] Tomomitsu Sasaki,[a] Nobuyuki Funato,[a] Hiroaki Takayanagi,
Lijun Wu,[b] Xian Li,[b] Masayuki Onda,[b] and Yoshihiro Harigaya[a]

[a]School of Pharmceutical Sciences, Kitasato University, Minato-ku, Tokyo 108,
Japan and [b]Shenyang College of Pharmacy, Wenhua-lu, Shenyang, China

Abstract- The absolute configuration of bruceine H was determined to be 1*S*, 5*S*, 7*R*, 8*R*, 9*R*, 10*S*, 11*R*, 12*S*, 13*R*, 14*R*, 15*R* by means of X-ray analysis of 15-*O*-acetylbruceine H 22-*p*-bromobenzoate

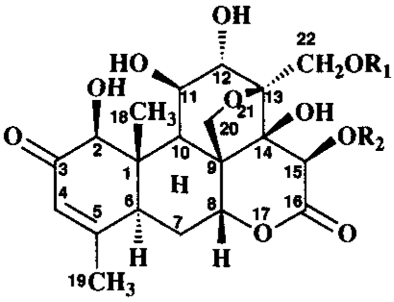
A number of quassinoids[1-8] have so far been isolated as bitter principles of Simaroubaceae plants. Among them, several quassinoids have been shown to posesses potent pharmacological activities, for examples, 13,18-dehydroglaucarubinone[3] with antitumor activity; undulatone,[4] bruceantin, bruceantinol,[5] bruceoside A, B[6] with antileukaemic activity; shinjulactone A[8] with potent cytotoxity. Furthermore, a new antileukaemic quassinoid glycoside, bruceoside C,[12] has been recently reported. Because of these important pharmacological activities and the difficulties to construct these highly oxygenated compounds, many synthetic chemists have made attention to total synthesis of the quassinoids.

Recently, total synthesis of racemic shinjulactone D[13] have been reported and followed from the asymmetric synthesis of simalikalactone D[14] in 1992. Inspite of the interesting target for isolation, structure determination and total synthesis, their absolute configurations have been followed from the experimentally proven triterpenoid biogenetic origin of the quassinoids.[15]

Previously, we have reported the absolute stereochemistry of bruceines D, E and H[16] having epoxymethylene bridge between C-8 and C-13 by a conbination of 2D nmr, nOe and CD spectroscopic analysis. Many of the quassinoids have so far been studied by X-ray analysis,[1, 4-11] and among them, there are two report[10, 11] about the quassinoid glucosides. One[11] of them concerns to the determination of the absolute stereochemistry of a quassinoid, having epoxymethylene bridge between C-8 and C-11, by X-ray analysis and isolating sugar moiety as D-glucose on enzymatic hydrolysis. But other reports[1, 4-10] have only descrived the relative stereochemistry.

In this paper, we wish to report the absolute structure of bruceine H (**1**) by X-ray analysis. After many efforts, we gained single crystals of 15-*O*-acetylbruceine H 22-*p*-bromobenzoate (**2**) suitable for X-ray analysis.

2 was prepared from *p*-bromobenzoyl chloride and pyridine in dry benzene, followed by acetylation with acetic



1 $R_1=R_2=H$
2 $R_1=p$-bromobenzoyl, $R_2=$ acetyl

Scheme 1

anhydride and pyridine in chloroform: Colorless needles, mp 270°C, FABms *m/z* 653, 651 ($M+1^+$), Calcd for $C_{29}H_{31}O_{12}Br$ 650. Crystals of **2** have grown from a solution in $CHCl_3$ by slow evaporation of the solvent. The structure was solved[17] by direct method and refined by full-matrix least-squares method. The final R factor based on the absolute structure shown in Figure 1 was 0.061 (Rw 0.051) for 1482 reflections with $I>3.00\ \sigma\ (I)$. The corresponding R factor for the enantiomer was 0.065 (Rw 0.055). Therefore we concluded that absolute configuration of the eleven asymmetric centers of **2** was 1*S*,5*S*,7*R*,8*R*,9*R*,10*S*,11*R*,12*S*,13*R*,14*R*,15*R* shown in Figure 1 which is same configuration as we previously proposed by nmr and CD spectroscopies.[16]

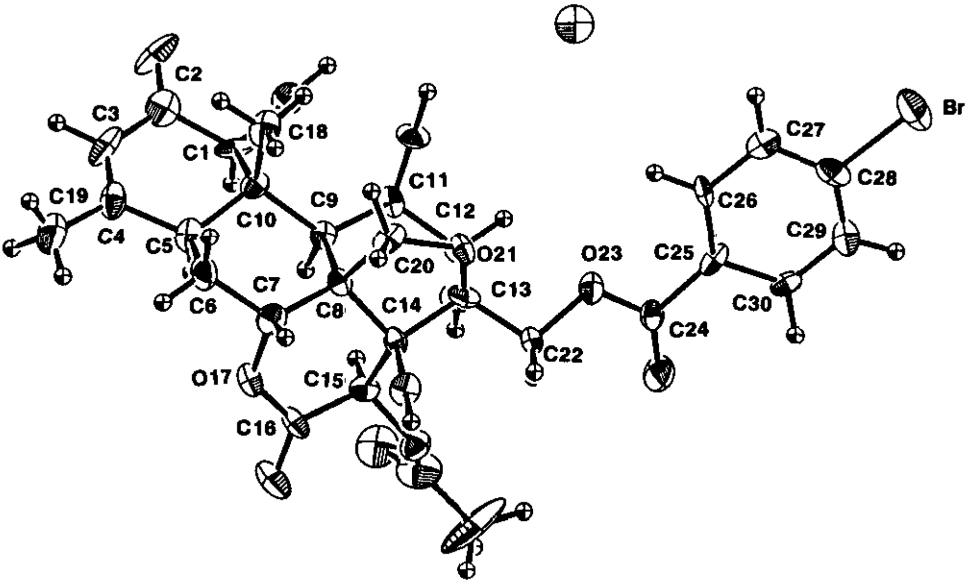


Figure 1 ORTEP Drawing of **2**

Though several reports have showed the ring conformations of the quassinoids,[7,8] there is no report of the conformational analysis of the quassinoids having epoxymethylene bridge between C-8 and C-13 except our report.[16] Polonsky already reported the X-ray analysis of 4'-*O*-acetylbruceine C,[7] having epoxymethylene bridge between C-8 and C-13 in it, but none of the conformations has been described. ORTEP drwawing with the atomic numbering systems showing the overall molecular conformation of **2** is given in Figure 1. The selected torsional angles are listed in Table 1. The ring junctions are the same as in all quassinoids (A/B *trans*, B/C *trans*, B/D *cis* and C/D *cis*) and the configurations of the hydroxyl substituents are 1β, 11β, 12α, 14β, 15β.

Each ring conformations are assumed as follows from tortional angles and perspective views about several angles. Ring A adopts a half chair form and the atoms, C(2),C(3),C(4),C(5) seem to be close to planar from the value of torsional angle (C(2)-C(3)-C(4)-C(5)=-8°). Ring B adopts a chair form but is slightly flattened about the atoms C(11) and C(12) from the torsional angles (C(8)-C(9)-C(11)-C(12)=39°, C(9)-C(11)-C(12)-C(13)= -38°). These results are assumed to be caused by repulsion between oxygen atoms in epoxymethylene ring and C(11) atom. Ring D adopts a half chair form from the torsional angle (C(15)-C(16)-O(17)-C(7)=-30°) caused by planar ester bond.

Table 1. Dihedral Angles (°) of **2**

A Ring		C Ring	
C10-C1-C2-C3	-42 (2)	C14-C8-C9-C11	-57 (2)
C1-C2-C3-C4	17 (3)	C8-C9-C11-C12	39 (2)
C2-C3-C4-C5	-8 (3)	C9-C11-C12-C13	-38 (2)
C3-C4-C5-C10	24 (2)	C11-C12-C13-C14	56 (2)
C4-C5-C10-C1	-47 (2)	C12-C13-C14-C8	-68 (2)
C5-C10-C1-C2	57 (2)	C13-C14-C8-C9	69 (2)
B Ring		D Ring	
C10-C5-C6-C7	-61 (2)	O17-C7-C8-C14	-48 (2)
C5-C6-C7-C8	49 (2)	C7-C8-C14-C15	65 (2)
C6-C7-C8-C9	-43 (2)	C8-C14-C15-C16	-60 (2)
C7-C8-C9-C10	47 (2)	C14-C15-C16-C17	41 (2)
C8-C9-C10-C5	-56 (2)	C15-C16-O17-C7	-30 (2)
C9-C10-C5-C6	64 (2)	C16-O17-C7-C8	33 (2)

This report is the first example about the absolute configuration of the quassinoids having epoxymethylene bridge between C-8 and C-13 by X-ray method. Asymmetric total synthesis of the quassinoids is now very interesting and desired subject for synthetic chemist owing to their important bioactivities. Accurate determination of the stereochemistry of bruceine H will be available for natural and synthetic chemistry in the near furture.

REFERENCES AND NOTES

1. G. Kartha and D. J. Haas, *J. Amer. Chem. Soc.*, 1964, **86**, 3630
2. a) J. Polonsky, Z. Baskevitch, B. C. Das, and J. Muller, *C. R. Seances Acad. Sci.*, Ser. C, 1968, **267**, 1346. b) J. Polonsky and J. Muler, *ibid.*, 1968, **268**, 1392.
3 J. Polonsky, Z. Jacqemin, and G. R. Petti, *Experientia*, 1978, **34**, 1122.
4. M. C. Wani and L. T. Harald, *Tetrahedron*, 1979, **35**, 17.
5. J. Polonsky and J. Varenne, *Tetrahedron Lett* ., 1980, **21**, 1853.
6. a) K. H. Lee, Y. Imakura, Y. Sumida, R. Y. Wu, I. H. Hall, and H. C. Haung, *J. Org. Chem.*, 1979, **44**, 2180. b) K. H. Lee, N. Hayashi, M. Okano, H. Hozaki, and M. Juichi, *J. Nat. Prod.*, 1984, **47**, 550.
7. J. polonsky, M. V. Varon, T. Prange, and C. Pascard, *Tetrahedron*, 1980, **36**, 2983.
8. a) J. Polonsky, Proc. Chem. Soc., 1964, 292. b) W. A. C. Brown and G. A. Sim, *ibid.*, 1964, 293.
9. C. Pascard, T. Prange, and J. Polonsky, *J. Chem. Res.*, 1977, 324.
10. S. Bhatnagar, J. Polonsky, T. Prange, and C. Pascard, *Tetrahedron Lett.*, 1984, **25**, 299.
11. T. Ohmoto, K. Koike, T. Prange, and C. Pascard, *Chem. Pharm. Bull.*, 1989, **3**
12. H. Fukamiya, M. Okano, and M. Miyamoto, *J. Nat. Products*, 1992, **55**, 468.
13. R. G. Gross, P. Grieco, and J. L. Collin, *J. Org. Chem*, 1991, **56**, 7167.
14. E. D. Moher, J. L. Collins, and P. A. Grieco, *J. Amer. Chem. Soc.*, 1992, **114**, 2764.
15. J. Polonsky, *Fortschr. Chem. Org. Naturstoffe*, 1973, **30**, 101.
16. a) X. Li, L. Wu, Y. Konda, M. Iguchi, H. Takahashi, Y. Harigaya, and M. Onda, *J. Heterocycl. Chem.*, 1989, **26**, 493. b) Y. Harigaya, Y. Konda, M. Iguchi, and M. Onda, *J. Nat. Prod.*, 1989, **52** 740.
17. Crystallographic Data of **2**: $C_{29}H_{31}O_{12}Br$ (MW), Orthorhobic, Space group $P2_12_12_12_1$ (#19), a=14.065(3)Å b=23.675(3) Å, c=9.639(3) Å, V=3210(1) A^3, Z=6, Dc=1.571 g/cm^3, (CuKα)=31.05 cm^{-1} Intensity data were collected at room temperature with graphite monochromated CuKα radiation (=1.54178 Å) on a Rigaku AFC-5R diffractometer.; $2\theta_{max}$=140.2. Of 3210 measured reflections, 1482 had I>3.00(I)σ and were used in the structure analysis. The structure was solved by direct methods and refined to R=0.061 (R_w=0.051) using the TEXAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985). The absolute configuration was confirmed by refining the inverted configuration which converted to higher residual of 0.065 (R_w=0.055). Atomic co-ordinates, bond length and thermal parameter have been deposited at the Cambridge Crystallographic Data Center.

Received, 1st November, 1993