Total Syntheses of the Structures Assigned to Salimine and Jerusalemine, Alkaloids from *Colchicum decaisnei* Boiss. (Liliaceae)

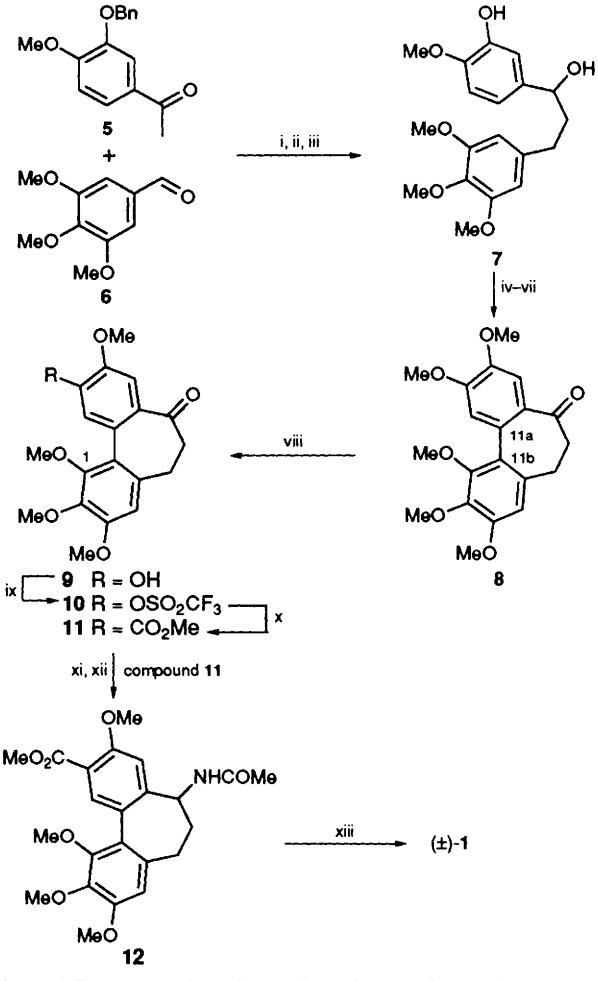
Martin G. Banwell,*[a] Marie-Anne Fam,[a] Robert W. Gable[a] and Ernest Hamel[b]

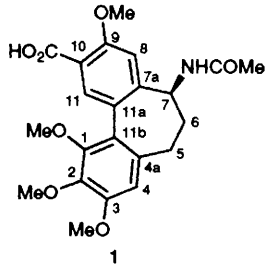
[a] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*
[b] *Laboratory of Molecular Pharmacology, DTP, DCT, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA*

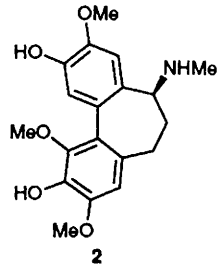
Total syntheses of the dibenzo[*a*,*c*]cycloheptylamines (±)-**1** and (±)-**2** have been developed; the spectroscopic properties of synthetic **2** match those reported for the alkaloid jerusalemine but compound **1** is different from the alkaloid salimine.

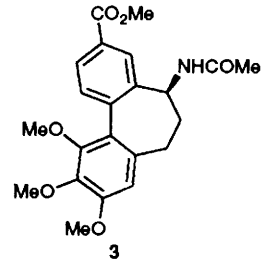
In 1991 Abu Zarga *et al.* described[1] the isolation of the alkaloids salimine, jerusalemine and suhailamine from the Middle Eastern species *Colchicum decaisnei* Boiss. (Liliaceae). On the basis of various spectroscopic studies, the dibenzo[*a*,*c*]cycloheptylamine structures **1–3**, respectively, were assigned to these compounds. It was further suggested that these alkaloids might be catabolites of colchicine **4** or 2-demethyldemecolcine. While a number of allocolchicinoid-like natural products have been isolated previously,[2] salimine and jerusalemine would appear to be the first members of this class which possess a C-10† substituent. In view of the continued interest in the synthesis and anti-mitotic properties of colchicinoids and allocolchicinoids,[2] we now describe the first total syntheses of (±)-**1** and (±)-**2**.

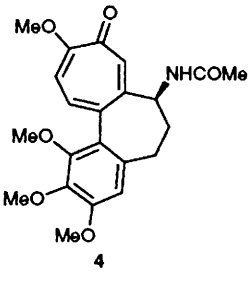
The reaction sequence used in the preparation of (±)-**1** is shown in Scheme 1. Thus, the known[3] acetophenone **5** was subjected to Claisen–Schmidt condensation with benzaldehyde **6** and the resulting chalcone (mp 105.5–106.5 °C, 92%)‡ treated with dihydrogen in the presence of palladium on carbon. The 1,3-diarylpropanone (mp 123–124 °C, 96%) thus formed was subjected to reaction with sodium borohydride and the alcohol **7**[4] (mp 147–149 °C, 96%) thereby obtained. Sequential treatment of compound **7** with lead tetraacetate then trifluoroacetic acid resulted in Umezawa cyclisation[5] and installation of the 11a–11b bond. The dibenzocycloheptan-7-ol[4] (mp 220–225 °C, 42%) formed in this way was *O*-methylated, and the resulting pentamethoxy alcohol (mp 149–150 °C, 72%) was oxidised with tetra-*n*-propylammonium perruthenate (TPAP)–*N*-methylmorpholine *N*-oxide (NMO)[6] to give ketone **8**[7] (mp 187–188 °C, 96%). Reaction of compound **8** with sodium ethanethiolate in hexamethylphosphoric triamide (HMPA)[8] at 100 °C afforded an inseparable *ca.* 1:1 mixture of the required phenol **9** and the regioisomer resulting from demethylation at C-1 (34% combined yield at 93% conversion). Treatment of this mixture with trifluoromethanesulfonic anhydride–*N*,*N*-dimethylaminopyridine (DMAP) resulted in formation of triflate **10** (mp 121–122 °C, 46%) which could be separated from its coproduced regioisomer (mp 148–150 °C, 22%) by HPLC. Palladium-catalysed methoxycarbonylation of compound **10** was readily achieved,[9] and the structure of the resulting keto ester **11** (mp 167–168 °C, 43% at 97% conversion) was







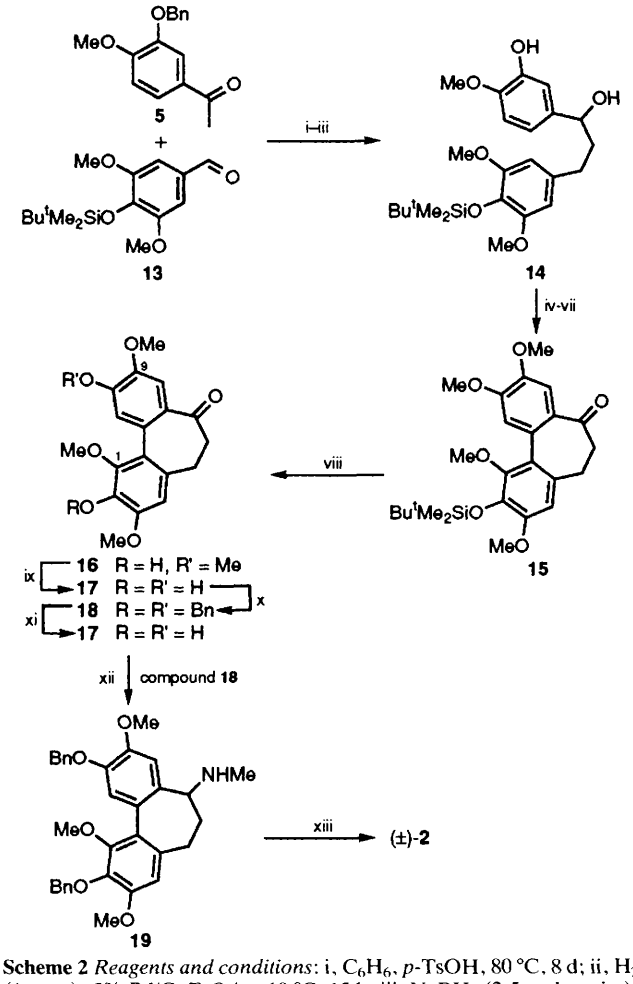




Scheme 1 *Reagents and conditions*: i, NaOH, MeOH, 18 °C, 3 d; ii, H_2 (1 atm.), 5% Pd/C, EtOAc, 18 °C, 15 h; iii, $NaBH_4$ (2.5 mol equiv.), THF–MeOH, 18 °C, 1.5 h; iv, $Pb(OAc)_4$ (1.2 mol equiv.), CH_2Cl_2, 18 °C, 1 h; v, CF_3CO_2H (50 mol equiv.), 1:1 C_6H_6–THF, 0 °C, 1 h; vi, $(MeO)_2SO_2$ (23 mol equiv.), K_2CO_3 (51 mol equiv.), Me_2CO, 18 °C, 21 h, then sat. aq. $NaHCO_3$, 18 h; vii, TPAP (7.5 mol%), NMO (3 mol equiv.), 4 Å molecular sieves, CH_2Cl_2, 18 °C, 24 h; viii, NaH (1.2 mol equiv.), EtSH (1.5 mol equiv.), HMPA, 100 °C, 9 h; ix, $(CF_3SO_2)_2O$ (1.5 mol equiv.), DMAP (3.2 mol equiv.), CH_2Cl_2, 0 °C, 1.5 h; x, $Pd(OAc)_2$ (1 mol equiv.), 1,1′-bis(diphenylphosphino)ferrocene (1 mol equiv.), DMF, Et_3N (2 mol equiv.), MeOH (20 mol equiv.), CO (g), 60 °C, 51 h; xi, NH_4OAc (10 mol equiv.), $NaBH_3CN$ (1 mol equiv.), MeOH, 60 °C (sealed tube), 8 d; xii, Ac_2O, pyridine, 18 °C, 0.5 h; xiii, LiOH (5 mol equiv.), MeOH, 50 °C, 10 h

established by single-crystal X-ray analysis [Fig. 1(*a*)].§ Reductive amination of compound **11**, using ammonium acetate and sodium cyanoborohydride,[10] produced an intermediate amino ester, which was immediately subjected to *N*-acylation using acetic anhydride–pyridine to afford the acetamido compound **12** (mp 228–230 °C, 45%). Hydrolysis of the ester moiety within this compound afforded, after acidic work-up, (±)-**1** (mp 218–221 °C, 75%).¶

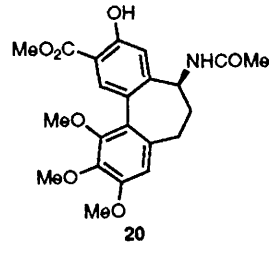
A closely related strategy was employed in the synthesis of (±)-**2** (Scheme 2). The *tert*-butyldimethylsilyl ether, **13**,[11] of syringaldehyde was subjected to Claisen–Schmidt condensation with acetophenone **5** under acidic conditions (*p*-TsOH, refluxing benzene) since attempts to effect the desired conversion with sodium hydroxide only resulted in desilylation of the former compound. The chalcone (mp 119–120 °C, 74%) produced in the acid-catalysed condensation reaction was immediately subjected to treatment with dihydrogen in the presence of palladium on carbon, and the 1,3-diarylpropanone (mp 125.5–126.5 °C, 97%) thus formed was reduced to the alcohol **14** (mp 125–127 °C, 97%) using sodium borohydride. Umezawa cyclisation[5] of this last compound gave the corresponding dibenzocycloheptenol (mp 215–217 °C, 54%) which was *O*-methylated using dimethylsulfate and potassium carbonate. The resulting tetramethoxy alcohol (mp 170–171 °C, 70%) was then oxidised to the ketone **15** (mp 148–150 °C, 96%). Removal of the *tert*-butyldimethylsilyl group in compound **15** was accomplished using tetra-*n*-butylammonium fluoride (TBAF), and the resulting phenol **16** (mp 168–169 °C, 70%) was subjected to treatment with sodium ethanethiolate. This afforded an inseparable *ca.* 3:1.5:1 mixture of diphenol **17** and the regioisomers where demethylation had occurred at C-1 and C-9, respectively. Benzylation of these compounds under standard conditions produced the corresponding mixture of dibenzyl ethers, which could be separated by HPLC. The required compound **18** (foam, 20%) obtained in this way was subjected to hydrogenolysis under standard conditions, and the structure of the resulting pure diphenol **17** (mp 169–171 °C, 80%) was established by single-crystal X-ray analysis [Fig. 1(*b*)].§ Completion of the synthesis of dibenzocycloheptylamine (±)-**2** involved reductive amination of ketone **18** using methylamine–sodium cyanoborohydride[12] followed by bis(debenzylation) of the resulting *N*-methylamine **19** (foam, 91%) to give the target compound (±)-**2** (mp 191–193 °C) in 88% yield.¶



Scheme 2 *Reagents and conditions*: i, C_6H_6, *p*-TsOH, 80 °C, 8 d; ii, H_2 (1 atm.), 5% Pd/C, EtOAc, 18 °C, 15 h; iii, $NaBH_4$ (2.5 mol equiv.), THF–MeOH, 18 °C, 1.5 h; iv, $Pb(OAc)_4$ (1.2 mol equiv.), CH_2Cl_2, 18 °C, 1 h; v, CF_3CO_2H (50 mol equiv.), 1 : 1 C_6H_6–THF, 0 °C, 1 h; vi, $(MeO)_2SO_2$ (23 mol equiv.), K_2CO_3 (51 mol equiv.), Me_2CO, 18 °C, 21 h, then sat. aq. $NaHCO_3$, 18 h; vii, TPAP (7.5 mol%), NMO (3 mol equiv.), 4 Å molecular sieves, CH_2Cl_2, 18 °C, 24 h; viii, Bu_4NF (1.2 mol equiv.), CH_2Cl_2, 0 °C, 2 h; ix, NaH (2 mol equiv.), EtSH (3 mol equiv.), 18-C-6 (0.5 mol equiv.), HMPA, 110 °C, 9 h; x, BnBr (2.2 mol equiv.), K_2CO_3 (4.0 mol equiv.), MeCN, 82 °C, 20 h; xi, H_2 (1 atm.), 5% Pd/C, EtOAc, 18 °C, 24 h; xii, $MeNH_2$ (6.0 mol equiv.), $NaBH_3CN$ (1.0 mol equiv.), AcOH (2 mol equiv.), MeOH, 60 °C (sealed tube), 5 d; xiii, H_2 (1 atm.), 5% Pd/C, HCl, EtOH, 18 °C, 16 h

A comparison of the spectroscopic data obtained on compound (±)-**2** with the analogous data reported[1] for jerusalemine led to the conclusion that these are one and the same compound. In contrast, comparison of the spectroscopic data derived from (±)-**1** with those reported[1] for salimine revealed significant differences, thus suggesting that the assigned structure for this alkaloid is incorrect. On the basis of mechanistic considerations,[1,13] it seemed appropriate to consider the isomeric structure **20** as being the correct one for salimine. Indeed, when an authentic sample of allocolchicinoid **20** was prepared [from (−)-colchicine][13] it became apparent that this compound is identical with salimine. It should also be noted that suhailamine[1] has been assigned the same structure as allocolchicine **3** but has different spectroscopic and physical properties from an authentic sample of **3**.[14] At this point the true structure of suhailamine remains unclear.

In order to gain some indication of their potential as anti-mitotic agents, allocolchicinoids (±)-**1** and (±)-**2** have been subjected to a tubulin binding assay.[15] Contrary to



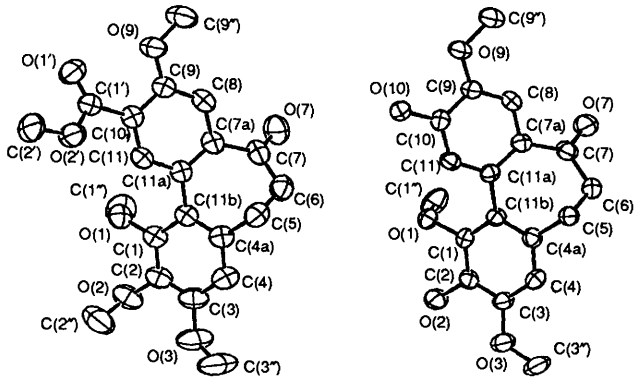


Fig. 1 ORTEP[17] drawings of compounds **11** and **17** (right) derived from X-ray crystallographic data

expectation,[2,15] neither of these compounds displayed inhibitory effects on tubulin polymerisation. Furthermore, compounds (±)-**1** and (±)-**2** were not cytotoxic for L1210 cells.

The Australian Research Council is thanked for financial support. M. A. F. is the grateful recipient of an Australian Post-Graduate Research Award. We thank Professor Atta-ur-Rahman (H. E. J. Research Institute of Chemistry, Karachi) for providing copies of the spectra of salimine and jerusalemine. Dr T. K. Lim is thanked for assistance in acquiring NMR spectral data.

Received, 1st August 1994; Com. 4/04710I

Footnotes

† In order to facilitate comparisons, the colchicine numbering scheme[2] has been used throughout this paper.

‡ All new compounds had spectroscopic data [IR, UV (where appropriate), NMR, mass spectra] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ *Crystallographic data* for **11**: $C_{21}H_{22}O_7$, M = 386.39, T = 293(1) K, triclinic, space group $P\bar{1}$, a = 9.0038(11), b = 10.5885(12), c = 10.884(2) Å, α = 93.514(13), β = 108.357(13), γ = 100.727(9)°, U = 959.6(2) Å^3, D_c (Z = 2) = 1.337 g cm^{-3}, $F(000)$ = 408, μ(Mo-Kα) = 1.01 cm^{-1}, no absorption correction, 3361 unique data, 2203 with $I > 2\sigma(I)$; conventional $R_1[I > 2\sigma(I)]$ = 0.0481, wR_2 [all data] = 0.1451, GOF [all data] = 1.078.

For **17**: $C_{18}H_{18}O_6$·MeOH, M = 362.37, T = 293(1) K, monoclinic, space group $P2_1$, a = 7.6786(11), b = 8.3016(12), c = 14.153(2) Å, β = 92.599(10)°. U = 901.3(2) Å^3, D_c (Z = 2) = 1.335 g cm^{-3}, $F(000)$ = 384, μ(Mo-Kα) = 1.02 cm^{-1}, no absorption correction, 1941 unique data, 1374 with $I > 2\sigma(I)$; conventional $R_1[I > 2\sigma(I)]$ = 0.0400, wR_2 [all data] = 0.0779, GOF [all data] = 1.042.

Data were measured on an Enraf-Nonius CAD4MachS diffractometer (graphite crystal monochromator, λ = 0.71073 Å), with $2\theta_{max}$ = 50°. Refinement was by full-matrix least squares methods on F^2 (SHELXL-93[16]) using all data, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ *Selected spectral data* for (±)-**1**; ^{13}C NMR (100 MHz, $^2H_6$-DMSO) δ 168.6, 167.1, 157.4, 152.4, 150.3, 145.9, 140.5, 134.7, 132.2, 125.6, 123.3, 118.7, 108.2, 107.3, 60.6, 60.5, 55.8, 55.7, 48.4, 38.3, 30.0 and 22.6; ^{1}H NMR (400 MHz, $^2H_6$-DMSO) δ 12.40 (br s, 1H, CO_2H), 8.41 (d, J = 8.8 Hz, 1H, NH), 7.63 (s, 1H), 7.07 (s, 1H), 6.78 (s, 1H), 4.55 (m, 1H, H7), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.48 (s, 3H, OMe), 2.52 (m, 1H), 2.19 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H) and 1.90 (s, 3H, COMe); MS m/z (EI, 70 eV) 414 (100%) [(M − H·)$^+$], 356 (50) [(M − $MeCONH_2$)$^{+\cdot}$]; ν_{max} (KBr) 3435 (br), 3278, 2938, 1637, 1612, 1555, 1460, 1407, 1238, 1100, 1053 cm^{-1}; λ_{max} (MeOH) 264 (sh, log ε 4.4) and 219 (4.5) nm; HRMS, [(M − H·)$^+$] 414.1544. $C_{22}H_{24}NO_7$ requires 414.1553.

For (±)-**2**; ^{13}C NMR (100 MHz, $^2H_6$-DMSO) δ 147.1, 146.5, 144.8, 143.8, 137.7, 131.8, 129.9, 127.2, 124.5, 116.9, 107.7, 107.5, 59.5, 59.3, 55.8, 55.4, 34.9 and 30.1 (one peak obscured or overlapping); ^{1}H NMR (400 MHz, $^2H_6$-DMSO) δ 8.61 (br s, 1H, OH), 8.30 (br s, 1H, OH), 7.09 (s, 1H), 6.79 (s, 1H), 6.61 (s, 1H), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.07 (dd, J = 11.2, 6.4 Hz, 1H, H7), 2.32 (dd, J = 12.7, 5.9 Hz, 1H), 2.20 (m, 1H), 2.17 (s, 3H, NMe), 1.99 (m, 2H) and 1.52 (m, 1H); MS m/z (EI, 70 eV) 345 (56%) (M$^{+\cdot}$), 328 (21) [(M − HO·)$^+$], 314 (100) [(M − MeO·)$^+$] and 299 (23); ν_{max} (KBr) 3353, 3313, 2935, 1603, 1497, 1453, 1312, 1265, 1215, 1105, 1080, 1040 and 791 cm^{-1}; λ_{max} (MeOH) 278 (sh, log ε 3.8), 266 (4.0) and 212 (4.5) nm; HRMS, M$^{+\cdot}$ 345.1565. $C_{19}H_{23}NO_5$ requires 345.1576.

References

1 M. H. Abu Zarga, S. S. Sabri, T. H. Al-Tel, Atta-ur-Rahman, Z. Shah and M. Feroz, *J. Nat. Prod.*, 1991, **54**, 936.
2 O. Boyé and A. Brossi, in *The Alkaloids*, ed. A. Brossi and G. A. Cordell, Academic, New York, 1992, vol. 41, pp. 125–176, and references therein.
3 Y. Inubushi, Y. Masaki, S. Matsumoto and F. Takami, *J. Chem. Soc. (C)*, 1969, 1547.
4 M. G. Banwell, J. N. Lambert, M. F. Mackay and R. J. Greenwood, *J. Chem. Soc., Chem. Commun.*, 1992, 974.
5 H. Hara, H. Shinoki, O. Hoshino and B. Umezawa, *Heterocycles*, 1983, **20**, 2155.
6 W. P. Griffith and S. V. Ley, *Aldrichchimica Acta.*, 1990, **23**, 13.
7 T. Kametani, S. Hirata and S. Shibuya, *Yakugaku Zasshi*, 1972, **92**, 1108 (*Chem. Abstr.*, 1972, **77**, 164298u).
8 G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1970, 1327; C. Hansson and B. Wickberg, *Synthesis*, 1976, 191.
9 S. Cacchi, P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1986, **27**, 3931.
10 R. M. Williams, P. P. Ehrlich, W. Zhai and J. Hendrix, *J. Org. Chem.*, 1987, **52**, 2615.
11 M. Cushman, D. Nagarathnam, D. Gopal, H.-M. He, C. M. Lin and E. Hamel, *J. Med. Chem.*, 1992, **35**, 2293.
12 R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.
13 M. A. Iorio, *Heterocycles*, 1984, **22**, 2207.
14 H. Fernholz, *Liebigs Ann. Chem.*, 1950, **568**, 63.
15 M. G. Banwell, J. M. Cameron, M. Corbett, J. R. Dupuche, E. Hamel, J. N. Lambert, C. M. Lin and M. F. Mackay, *Aust. J. Chem.*, 1992, **45**, 1967.
16 G. M. Sheldrick, SHELXL-93, *J. Appl. Cryst.*, 1994, in the press.
17 C. K. Johnson, ORTEPII, Report ORNL-5138 Oak Ridge National Laboratory, Tennessee, USA, 1976.