

SYNTHESIS OF 7 α - AND 17-BROMONORAMBREINOLIDES FROM NORAMBREINOLIDE

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Abstract: A mixture of 7 α - and 17-bromonorambreinolides was obtained on treatment of the mixture of isomeric methyl bicyclohomofarnesenoates, the norambreinolide transesterification product, with NBS and H₂O₂. The structure of 7 α - and 17-bromonorambreinolides was elucidated on the basis of spectral data. The structure of 17-bromonorambreinolide was confirmed by its reduction with LiAlH₄ into sclaradiol, and that of 7 α -bromonorambreinolide by X-ray analysis.

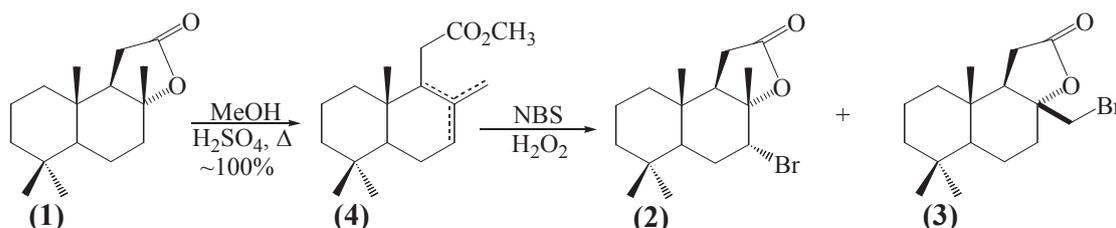
Keywords: 7 α - and 17-bromonorambreinolides, synthesis, X-rays analysis.

INTRODUCTION

Norambreinolide [sclareolide, 8 α ,12-epoxi-14,15,16,17-tetranorlabdane-12-one] (1) is a valuable, commercially available chiron, formed on oxidative degradation of a series of labdanic diterpenoids [1]. It served as starting compound in the synthesis of many drimanic sesquiterpenoids [2-5] and some higher terpenoids [6,7]. However, to a certain extent, synthetic possibilities of the norambreinolide are limited because in its molecule there are only two functional groups, at C(8) and C(12). In connection with this it was of interest to obtain its derivatives with functional groups at other carbon atoms of cycle B and especially at hardly accessible position C(17).

RESULTS AND DISCUSSIONS

Herein, we described a short synthesis of the mixture of 7 α - and 17-bromonorambreinolides (2) and (3) from norambreinolide (1). The latter was transformed according to the known procedure [8] in high yield into the mixture of methyl bicyclohomofarnesenoates (4) (scheme 1). On treatment of this esters mixture in mild conditions with NBS and an aqueous solution of hydrogen peroxide a mixture of two products was formed which were separated by column chromatography on SiO₂. Their structure was determined on the bases of analytical and spectral data and for the more polar compound was also confirmed by X-ray analysis.

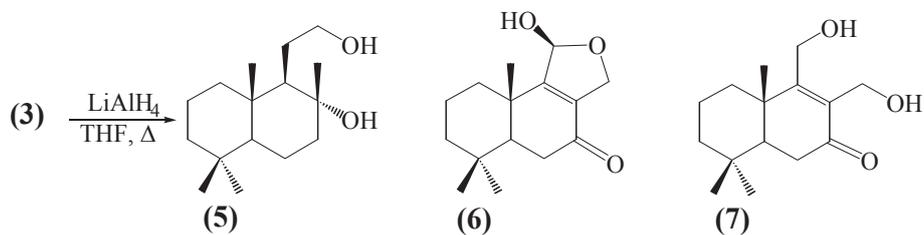


Scheme 1.

The less polar product according to the elemental analysis has the composition C₁₆H₂₅BrO₂. Its IR spectrum exhibits absorption bands of the C-Br-bond at 653 cm⁻¹ and a γ -lactone at 1793 cm⁻¹. In the ¹H NMR spectrum of this compound three-protons singlet signals of three tertiary methyl groups are presented, one methyl group less than in the starting compound (1). In the low field region of its ¹H NMR spectrum besides the signals of -CH-CH₂CO-group, there are at 3.36 and 3.37 ppm two one proton doublets belonging to the AB-system of the group \equiv C-CH₂Br. Since the signal of C(10)-CH₃ group in the ¹H NMR spectrum of investigated bromolactone was not shifted downfield in comparison with its signal in the spectrum of norambreinolide (1) [9], the -CH₂Br group is placed on the β -side of molecule and has axial configuration. This conclusion was confirmed also by chemical data: on the reaction of investigated bromolactone with LiAlH₄ in THF the known diol (5) was obtain (scheme 2). Thus, on this treatment not only the lactone group, but also the CH₂Br group were reduced. The summary of the above mentioned data proved that the studied bromolactone is the 17-bromonorambreinolide (3). It contains the bromine atom at a hardly accessible position and can served for the synthesis of terpenoids in which the C(17) carbon atom is functionalized (see, for example, the articles [10-15]).

Further elution with the same solvent yielded the major reaction product, having the same elemental composition as compound (3) (scheme 1). Its IR spectrum contains absorption bands characteristic of a C-Br bond at 657 cm⁻¹ and a

γ -lactone group at 1791 cm^{-1} . In the low field portion of ^1H NMR spectrum besides the signals of $\text{C}(11)\text{H}_2$ -group there are the signals of the proton at $\text{C}(7)$ carbon atom, bonded with the bromine atom. In such a way the major reaction product is the 7α -norambreinolide (1). The structure of this compound was confirmed not only by spectral data but also by X-ray analysis.



Scheme 2.

Crystal structure determination

The structure of compound (2) has been confirmed by X-ray single crystal method. X-Ray data were collected on a KUMA Diffraction KM4 at 100 K using graphite-monochromated Cu-K α radiation. Lattice parameters elementary were obtained from least-squares refinement of 25 with $22 \leq 2\theta \leq 52$. There was no intensity decay during data collection. Structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares methods based on F^2 (SHELXL-97) [16]. Lorentz and polarization corrections were applied for diffracted reflections. The non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically. The crystallographic data and details of structure refinement are listed in Table 1. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC NO. 646964. Copy of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or <http://www.ccdc.cam.ac.uk>).

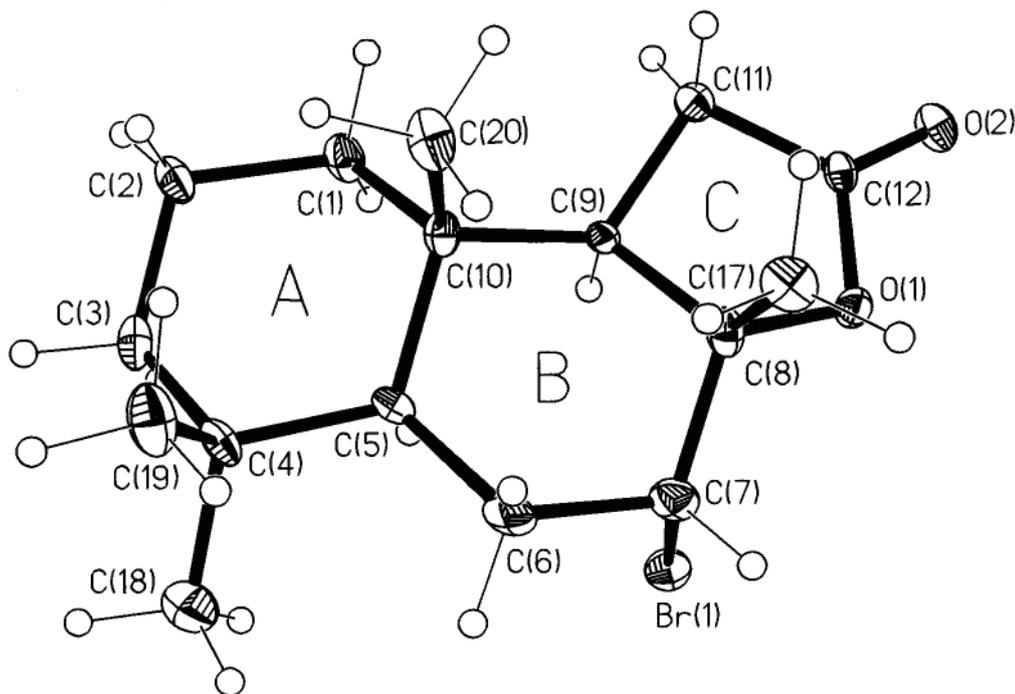


Figure 1.

View of molecule in two projections with numbering scheme is shown in Figure 1 and 2. X-ray study unambiguously proves the molecular structure of (2). Both cyclohexyl rings, A and B have chair conformation. Atoms C(1), C(2), C(4), C(5) are coplanar within $\pm 0.018\text{ \AA}$. The displacement of atoms C(3) and C(10) from this plane are $-0.625(9)$ and 0.700 \AA respectively. The Cremer-Pople (CP) parameters [17] for cycle A: $\Theta=4.9(6)^\circ$, $\varphi=-11(8)^\circ$ and $Q=0.567(7)\text{ \AA}$. In cycle B the atoms C(8) and C(5) displace at $0.695(10)$ and $-0.683(9)\text{ \AA}$ out of the plane of C(6)C(10)C(9)C(7) atoms, which are coplanar within $\pm 0.013\text{ \AA}$. CP parameters for cycle B are $\Theta=2.4(6)^\circ$, $\varphi=-101(16)^\circ$ and $Q=0.592(7)\text{ \AA}$. Methyl groups at atoms C(8) and C(10) reside axial position and at C(4)-axial C(19) and equatorial C(18) positions. Such arrangement of methyl groups lead to stressed 1,5-intramolecular contacts $\text{C}(19)\cdots\text{C}(20)=3.23(1)$

and $C(20)\cdots C(17)=3.14\text{\AA}$. The similar stressed intramolecular contacts have been found in related compounds having the same skeleton, namely in the structures of 11,12-epoxydrim-8-en-11 β -ol-one (6) [18] and 11,12-dihydroxydrim-8-en-one (7) [19] where such intramolecular contacts equal 3.32 and 3.35 \AA , respectively. One can suppose that such contacts always take place in molecules of this type and cause the slight distortion of tetrahedral angles at carbon atoms of molecular skeleton. Bromine atom reside axial position at C(7) opposite to axial methyl groups (Fig. 2). The distance $C(7)\text{-Br}(1)$ equals 1.973(7) \AA . The carbon-carbon distances in cyclohexyl rings are in the range 1.521(8)-1.575(9) \AA , $C\text{-CH}_3$ - 1.517(9)-1.535(9) \AA . Tetrahydrofuran cycle C has an envelop conformation. Displacement of atoms C(9) and O(2) from the mean plane of coplanar within $\pm 0.048\text{\AA}$ remaining atoms of five membered cycle equal $-0.655(10)$ and $-0.16(10)\text{\AA}$, respectively. The puckering parameters (CP) of cycle C $\varphi=-118.1(7)^\circ$ and $q_2=0.430(7)\text{\AA}$ close to value $\varphi=108^\circ$ for ideal envelop. The distances in cycle C $C(12)\text{-O}(2)=1.215(8)\text{\AA}$, $O(1)\text{-C}(12)=1.354(8)\text{\AA}$, $O(1)\text{-C}(8)=1.468(8)\text{\AA}$, $C(12)\text{-C}(11)=1.508(8)\text{\AA}$ indicate π -conjunction in the fragment $O(2)C(12)O(1)$. Endo-cyclic angle at O(1) equals $108.2(6)^\circ$.

The majority of intermolecular contacts in crystal are Van der Waals type. The shortest contacts are $Br(1)\cdots C(11)=3.798(8)\text{\AA}$, $Br(1)\cdots C(17)=3.843(9)\text{\AA}$, $O(1)\cdots C(7)=3.435(9)\text{\AA}$, $O(1)\cdots C(17)\text{\AA}$ and $O(2)\cdots C(20)=3.342\text{\AA}$. The last described contacts may be rate as $C\text{-H}\cdots O$ hydrogen bond [20], $H\cdots O=2.50\text{\AA}$ and angle $C\text{-H}\cdots O=144^\circ$. The shortened contacts take place between two-fold screw axis and translations a and b related molecules.

The nearest contacts between the neighboring in molecules of the crystal have basically Van-der-Vaals character. The shortest among them are distances $Br(1)\cdots C(11)=3.798(8)\text{\AA}$, $Br(1)\cdots C(17)=3.843(9)\text{\AA}$, $O(1)\cdots C(7)=3.435(9)\text{\AA}$, $O(1)\cdots C(17)=3.527\text{\AA}$ and $O(2)\cdots C(20)=3.342\text{\AA}$. Last value can be considered as $C\text{-H}\cdots O$ hydrogen bond [20] with the distance $H\cdots O=2.50\text{\AA}$ and an angle at H equals to 144° . The short intermolecular contacts are observed for the molecules connected by an 2_1 axis with basic, and also with distant from her on translation on axes X and Y.

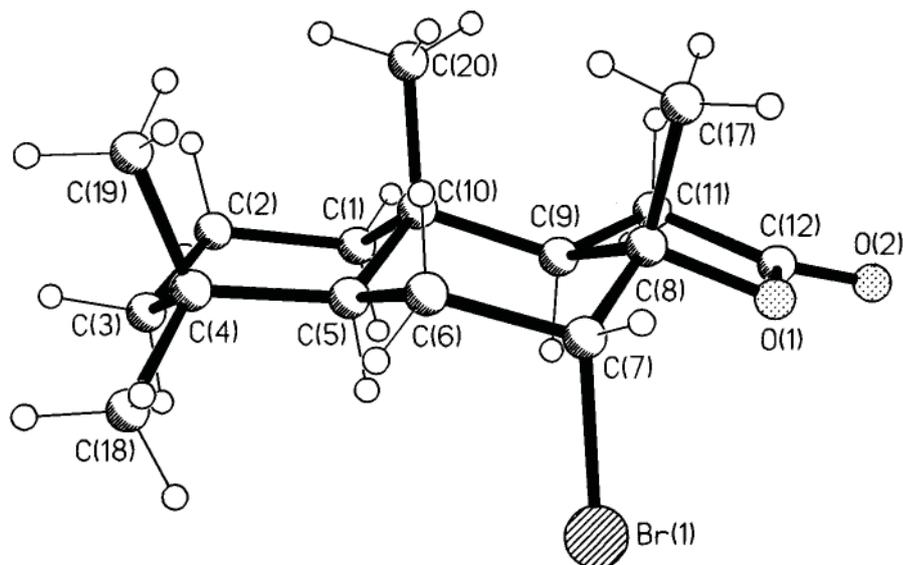


Figure 2

EXPERIMENTAL SECTION

Melting points (mp) were determined on a Boetius hot stage. IR spectra were obtained on a Specord 74 spectrometer in CCl_4 . NMR 1H and ^{13}C spectra were recorded on a Bruker WM (300.13 and 75.32 MHz) spectrometers in $CDCl_3$. Chemical shifts are given in parts per million values in δ scale with $CHCl_3$ as reference (set δ_H at 7.24 ppm and δ_C 77.00 ppm) and coupling constants in Hertz. Optical rotations were determined on a Perkin-Elmer 241 polarimeter using $CHCl_3$ as solvent. For analytical TLC the Сорбфил plates were used. Column chromatography was carried out on Across silica gel (60-200 mech).

Synthesis of 7 α - and 17-bromonorambreinolide (2) and (3). To the solution of 300 mg (1.14 mmol) of esters mixture (4), prepared according to the procedure [8], in 3 mL of $CHCl_3$, was added on stirred at $22^\circ C$ 410 mg (2.27 mmol) of NBS and then was dropped 0.2 mL of 30% H_2O_2 . The mixture was stirred at the same temperature up to the finish of the reaction (24 hours, controlled by TLC). Then the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3x15 mL). The extract was washed with 0.1 N solution of $Na_2S_2O_3$ (20 mL), water (20 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The oil residue (400 mg) was chromatographed

on a column with silica gel (40 g). Elution with the mixture of benzene : ethylacetate 96:4 gave 82.2 mg (yield 22 %) of 17-bromonorambreinolide (3) was obtained, mp 107-108°C (from petroleum ether), $[a]_D^{22} - 11.3^\circ$ (c 0.97), Found (%): C, 58.08; H, 8.12; Br, 24.39. $C_{16}H_{25}BrO_2$. Requires (%): C, 58.36; H, 7.65; Br, 24.27. IR, ν/cm^{-1} : 653 (Br), 1793 (γ -lactone). 1H NMR, δ : 0.87 (s, 3H, C(20)H₃), 0.89 (s, 3H, C(18)H₃), 0.90 (s, 3H, C(19)H₃), 1.10-2.23 (m, 12H), 2.39 (dd, 1H, J=1.2, 18.4 Hz), 2.68 (dd, 1H, J=8.8; 18.4 Hz, C(11)H₂), 3.36 (d, 1H, J=10.88 Hz) and 3.37 (d, 1H, J=10.88 Hz, AB-system, C(17)H₂). ^{13}C NMR, δ : 14.98, 17.86, 18.03, 21.91, 30.60, 31.48, 33.11, 33.22, 35.98, 40.17, 40.99, 41.62, 50.15, 50.99, 85.97, 176.56.

Further elution with the same solvent afforded 179.4 mg (yield 48.1%) of 7 α -bromonorambreinolide (2), mp 187-188°C (from petroleum ether), $[a]_D^{22} - 31.3^\circ$ (c 0.8). Found (%): C, 58.34; H, 8.10; Br, 24.32. $C_{16}H_{25}BrO_2$. Requires (%): C, 58.36; H, 7.67; Br, 24.27. IR, ν/cm^{-1} : 657 (Br), 1791 (γ -lactone). 1H NMR, δ : 0.87 (s, 3H, C(20)H₃), 0.92 (s, 3H, C(18)H₃), 0.94 (s, 3H, C(19)H₃), 1.58 (s, 3H, C(17)H₃), 1.00-2.30 (m, 10H), 2.49 (dd, 1H, J=3.96, 18.4 Hz), 2.75 (dd, 1H, J=10.44, 18.4 Hz, C(11)H₂), 4.61 (dd, 1H, J=7.53, 9.90 Hz, C(7)). ^{13}C NMR, δ : 16.74, 18.01, 21.13, 27.95, 30.50, 31.15, 32.19, 33.49, 36.53, 41.48, 41.99, 49.76, 55.80, 55.89, 87.35, 175.44.

REDUCTION OF 17-BROMONORAMBREINOLIDE (3) WITH LIALH₄

To the solution of 10 mg (0.03 mmol) of 17-bromonorambreinolide (3) in 2 mL of anhydrous THF 4.6 mg (0.012 mmol) of LiAlH₄ was added, and the reaction mixture was refluxed for 1 h (control by TLC). The excess of LiAlH₄ was destroyed by ethyl acetate, the mixture was treated with 5% solution of H₂SO₄ and extracted with diethyl ether (3x5mL). The extract was washed with water (2x10 mL), dried with anhydrous Na₂SO₄, filtered and solvent removed under reduced pressure. The residue was recrystallized from the mixture of petrol ether and AcOEt (4:1), to give 5 mg of known diol (5), m.p. 130-131°C, which was identified by comparison with the authentic sample.

Table 1

Crystal data and structure refinement for 7 α - bromonorambreinolide (2)

Empirical formula	$C_{16}H_{25}BrO_2$
Formula weight	329.27
Temperature, K	100(2)
Wavelength, Å	1.5418
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	
<i>a</i> , Å	7.871(1)
<i>b</i> , Å	7.773(2)
<i>c</i> , Å	12.471(2)
β , deg.	91.00(1)
<i>V</i> , Å ³	762.9(3)
<i>Z</i> , Calculated density, Mg/m ³	2, 1.433
Absorption coefficient, mm ⁻¹	3.634
<i>F</i> (000)	344
Crystal size, mm	0.50 x 0.10 x 0.10
θ -range for data collection, deg.	3.54 - 72.24
Limiting indices	$-9 \leq h \leq 0, 0 \leq k \leq 9, -15 \leq l \leq 15$
Reflections collected / unique, [<i>R</i> _{int}]	1707 / 1595, [0.0541]
Completeness to $\theta = 72.24$ deg.	97.7 %
Data / restraints / parameters	1595 / 1 / 176
Goodness-of-fit on <i>F</i> ²	1.030
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> 1 = 0.0365, <i>wR</i> 2 = 0.0867
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0607, <i>wR</i> 2 = 0.0956
Absolute structure parameter	-0.05(4)
Largest diff. peak and hole, e \cdot Å ⁻³	0.540 and -0.645

REFERENCES

- [1] Vlad, P.F.; Koltza, M.N.; *Synthesis and Application of Odorous Compounds from Labdane Diterpenoids*, Kishinev, *Shtiintsa*, 1988, 184 p. (In Russian).
- [2] Jansen, B.J.M.; de Groot A.. *Nat. Prod. Rep.*, 1991, 8, 319-337.
- [3] Vlad, P.F.; Koltza, M.N.; Mironov, G.N. *Russ. Chem. Bull.*, 1997, 46, 855-873.
- [4] Jansen, B.J.M.; de Groot A.. *Nat. Prod. Rep.* 2004, 21, 449-477.
- [5] Vlad, P.F. Synthetic investigation in the field of drimanic sesquiterpenoids in „*Studies of Natural Products Chemistry, Bioactive natural products*” (Part II); Elsevier: Amsterdam, 2006, 33, pp 393-432.
- [6] Corey, E.J.; Sauers, R.R. *J. Am. Chem. Soc.* 1959, 81, 1739-1743.
- [7] Vlad, P.F.; Kuchkova, K.I.; Aryku, A.N.; Deleanu, K. *Russ. Chem. Bull.* 2005, 54, 2656-2658.
- [8] Stoll, M.; Hinder, M. *Helv. Chim. Acta.* 1954, 37, 1859-1866.
- [9] Weyerstahl, P.; Marschall, H.; Weirauch, M.; Thefeld, K.; Surburg, H. *Flavour. Fragr. J.* 1998, 13, 295-318.
- [10] De Pascual Teresa J.; Urones, J. G.; Marcos, I.S.; Martin, D.D.; Alvarez, V.M. *Phytochemistry*, 1986, 25, 711-713.
- [11] Jakupovic, J.; Schuster, A.; Wasshausen, D.C. *Phytochemistry*, 1991, 30, 2785-2787.
- [12] Urones, J.G.; Marcos, I.S.; Basabe, P.; Diez, D.; Garrido, N.M.; Alonso, C.; Oliva, I.M.; Lithgow, A.M.; Moro, R.F.; Sexmero, M J.; Lopez, C. *Phytochemistry*, 1994, 35, 713-719.
- [13] Lee, I.-S.; Ma, X.; Chai, H.-B.; Madulid, D.A.; Lamont, R.B.; O'Neill, M.J.; Besterman, J.M.; Farnsworth, N.R.; Soejarto, D.D.; Cordell, G.A.; Pezzuto, J.M.; Kinghorn, A.D. *Tetrahedron*, 1995, 51, 21-28.
- [14] Joshi, B.S.; Hegde, V.R.; Kamat, V.N. *Phytochemistry*, 1996, 42, 761-766.
- [15] Zoretic, Ph.A.; Fang, H.; Ribeiro, A.A.; Dubay, G. *J.Org.Chem.*, 1998, 63, 1156-1161.
- [16] Sheldrick, G.M. SHELXL-93, *Program for refining crystal structure*, Univ. of Gottingen, 1993.
- [17] Cremer, D.; Pople, J.A. *J. Am. Chem. Soc.*, 1975, 97, 1354-1358.
- [18] Kravtsov, V.Kh.; Simonov, Yu.A.; Gorinchoi, E.K.; Koltza, M.N.; Vlad, P.F. *Crystallogr. Rep.*, 2000, 45, 789-791.
- [19] Kravtsov, V.Kh.; Gorinchoi, E.K.; Mironov, G.N.; Koltza, M.N.; Simonov, Yu.A.; Vlad, P.F. *Crystallogr. Rep.*, 2000, 45, 258-260.
- [20] Steiner, T. *Cryst. Rev.* 1996, 6, 1-51.