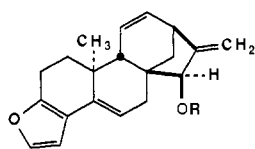
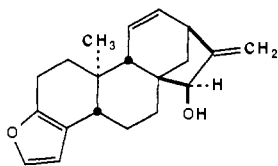


stereochemistry of **13** were confirmed unambiguously by 500-MHz



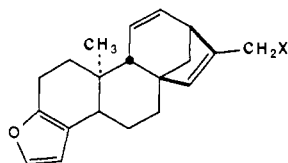
13 R = Bz
14 R = H

¹H NMR studies including spin decoupling and NOE measurements and also follow from the conversion to cafestol (**1**).¹¹ The pentacycle **13** is quite sensitive to acids and is even unstable in chloroform solution, apparently because of the vinyl furan subunit. Debenzylation of **13** was carried out by reaction with 15 equiv of lithium in 2:1 liquid ammonia-THF containing 7 equiv of ethanol at -78 °C for 30 min to give unsaturated alcohol **14** (100%). Alcohol **14** was further reduced with 5 equiv of sodium in 2:1 liquid ammonia-THF containing 5 equiv of water at -78 °C for 10 min to provide trans fused products **15** (90% yield, ratio of trans to cis product >95:5).¹²



15

The 11,12-double bond of **15**, though useful for the synthesis of 11-functionalized kaurenes, had to be reduced for the synthesis of cafestol itself. This operation as well as adjustment of functionality on the 16,17-bridge was conducted as follows. Alcohol **15** was converted to the allylic primary iodide **16** by mesylation



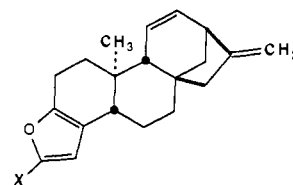
16 X = I
17 X = NHNH₂

(excess mesyl chloride and triethylamine in THF at -50 °C for 40 min) and subsequent reaction with powdered zinc iodide in methylene chloride at 23 °C for 2 h (72% overall yield). Treatment of iodide **16** with excess hydrazine (97%) in 1:1 dimethoxyethane-*tert*-butyl alcohol for 30 min at 23 °C provided the corresponding hydrazine (**17**, 100%) which after isolation but without purification was stirred in methylene chloride solution with oxygen for 7 h to give diene **18** (70% overall from **16**). This useful procedure for overall deoxygenation of **15** to form **18** was developed on the expectation that the allylic hydrazine **17** should be converted to **18** by oxidation, RNHNH₂ → RN=NH, followed by 1,5-sigmatropic rearrangement of hydrogen with loss of nitrogen. At this stage the furan ring was protected (against hydrogenation)¹³ by lithiation (*tert*-butyllithium in THF at -40 °C for 30 min) and reaction with triisopropylsilyl triflate to give **19** (90% yield). Conversion **19** to **1** in 55% overall yield was accomplished by the sequence: (1) selective hydroxylation of the

(11) The cyclization to form the kaurene system is a difficult one for steric reasons, success depending crucially on substrate structure. This facet of our research will be dealt with in a separate publication.

(12) Water is critical to the stereochemical outcome of this interesting reduction. Reduction of **14** with lithium in anhydrous liquid ammonia-THF at -78 °C affords stereoselectively the cis fused stereoisomer of **15** (72% isolated yield). It is possible that the stereoisomers are formed from different intermediates.

(13) See: Corey E. J.; Rücker, C. *Tetrahedron Lett.* 1982, 23, 719.



18 X = H
19 X = Si(iPr)₃

exocyclic double bond using osmium tetroxide in THF at 23 °C for 5 h, (2) hydrogenation of the 11,12-double bond with hydrogen (65 psi) and 5% Rh-Al₂O₃ catalyst in THF at 23 °C for 30 h, and (3) desilylation (stirring with 5:5:1 THF-acetonitrile-48% hydrofluoric acid at 23 °C for 3.5 h). The synthetic (±)-**1** so obtained was identical with an authentic sample of naturally derived cafestol¹⁴ with regard to silica TLC chromatographic mobility with use of several solvent systems, 500-MHz ¹H NMR, infrared, and mass spectra.

Several aspects of the synthesis of (±)-cafestol as described above are worthy of note. First, synthesis of chiral **7** either by enantioselective alkylation or resolution of the corresponding racemic acid, which should be realizable, would provide a route to the natural form of cafestol. The cyclization of **12** to **13**, which leads to the kaurene system directly and stereospecifically, demonstrates a new and versatile approach for the synthesis of this large class of diterpenes. Finally, the stereospecific reduction of **14** to either trans or cis fused products, the conversion of **15** to **18**, and the use of triisopropylsilyl as a protecting group in hydrogenation each illustrate useful new methodology.¹⁵

Supplementary Material Available: Listing of experimental data for compounds **1-19** (3 pages). Ordering information is given on any current masthead page.

(14) We are grateful to Prof. Carl Djerassi of Stanford University for a generous gift of cafestol.

(15) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Two-Directional Chain Synthesis: The Enantioselective Preparation of *Syn*-Skipped Polyol Chains from Meso Precursors

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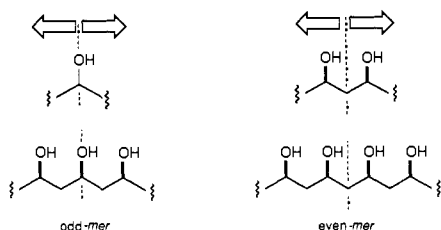
Gayle Schulte

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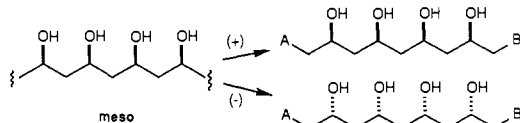
Received March 11, 1987

There are several attractive features of the chain synthesis strategy that involves the simultaneous homologation of a nascent chain in two directions.¹ This method offers the opportunity to reduce the total number of transformations required to complete a synthesis relative to the one-directional alternative. A problem intrinsic to this strategy is that, in most cases, the termini of the chain will require differentiation. If the homologated chain is meso, terminus differentiation will necessitate an enantiotopic group selective reaction.

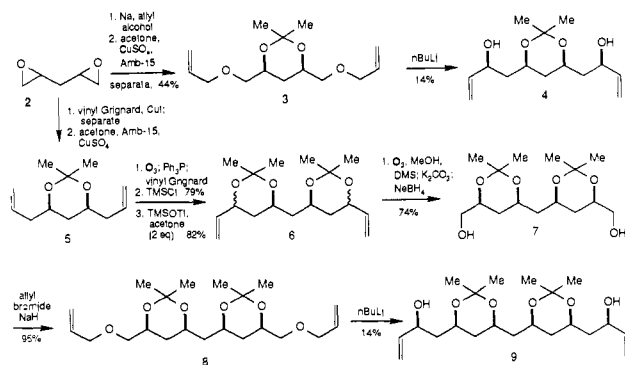
(1) For a discussion of the two-directional chain synthesis strategy, see: Schreiber, S. L. *Chem. Scr.*, in press.

Scheme I Strategy for *Syn*-Skipped Polyol Synthesis1. Two-directional synthesis of a *meso syn* hydroxylated polymer

2. Differentiation of the enantiotopic termini to provide either enantiomer

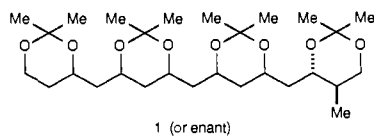


Scheme II



We recently described an important feature of *addition* reactions that proceed with enantiotopic group and diastereotopic face selectivity.² These terminus-differentiating reactions result in the formation of products with enhanced levels of enantiomeric purity³ by coupling a kinetic resolution to an asymmetric synthesis.⁴ In this communication, a two-directional chain synthesis of skipped polyol fragments found within members of the polyene macrolide class⁵ is described that utilizes a group and face selective Sharpless asymmetric epoxidation reaction⁶ to achieve terminus differentiation. The strategy allows an advanced *meso* (class A)¹ chain to be converted into either antipode of the chiral product with enhanced levels of enantiomeric purity.

As part of our structural and synthetic investigations of the polyene macrolide class, we desired a method for the preparation of skipped polyol chains such as the mycotocin A⁷ degradation product 1.⁸ Little information is available concerning the absolute



(2) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. See, also: (i) Takano, S.; Sakurai, K.; Hatakeyama, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. (ii) Jager, V.; Schroter, D.; Hafele, B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 87. (iii) Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791.

(3) The term "enhanced" refers to the level of purity relative to that expected for the simple face selective addition reaction.

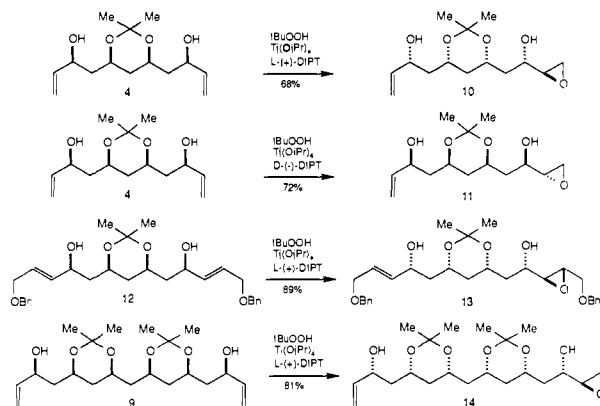
(4) The coupling of a kinetic resolution to an asymmetric synthesis in an enantiotopic group selective reaction was first demonstrated with an enzyme mediated hydrolysis: Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. See, also: reference cited in ref 2.

(5) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Biology and Practice*; Omura, S., Ed.; Academic: New York, 1984; pp 351-404.

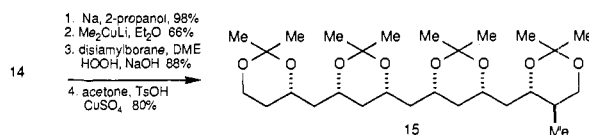
(6) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(7) Wasserman, H. H.; Van Verth, J. E.; McCaustland, D. J.; Barowitz, I. J.; Kamber, B. *J. Am. Chem. Soc.* **1967**, *89*, 1535.

Scheme III



Scheme IV



stereostructure of members of this class; hence, synthetic efforts have been directed to likely candidates for the natural stereoisomeric composition.⁹ On the basis of the structural analogies to amphotericin B, the single member of this class whose absolute stereostructure is known, the suggestion has been made that even distere relatives (e.g., mycotocin A) may contain the all *syn* polyol stereochemistry.^{9c,d,g,h} When our preliminary attempts to utilize X-ray crystallographic methods for structure elucidation were unsuccessful, we decided to compare degradation products from mycotocin A⁸ to stereodefined fragments prepared from synthesis.

A generalized schematic for the enantiodivergent synthesis of *syn*-skipped polyol chains related to 1 is presented in Scheme I. The two-directional homologation of an achiral carbinol or diol results in elongated polyol chains (odd-mer or even-mer, respectively). The mirror plane of symmetry renders the termini of the *meso* (undifferentiated) chain enantiotopic; group selective reactions can deliver either antipode of the differentiated product ($A \neq B$).

The two-directional synthesis of even-mers 4 and 9 is depicted in Scheme II. Ring opening of the bisepoxide 2¹⁰ with allyl alcohol and acetalization with acetone provided 3. The two-directional 1,2-Wittig rearrangement of 3 provided the all *syn* tetraol derivative 4 (>10:1).¹¹ The acetonide 5, available from 2 *via* the copper-catalyzed Grignard ring opening of 2, was converted to a mixture of stereoisomeric bisacetone 6. To achieve complete acetonide formation from all isomeric diol-monoacetonide precursors, an adaptation of Noyori's procedure was required for acetal formation was required.¹² The method of "ancillary stereocontrol",¹³ coupled with the ozonolysis reaction, produced

(8) Unpublished results of M. T. Goulet.

(9) (a) Nicolau, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (b) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873. (c) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (d) Kiyooka, S.-I.; Sasaoka, H.; Fujiyama, R.; Heathcock, C. H. *Tetrahedron Lett.* **1984**, *25*, 5331. (e) Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 75. (f) Oppong, I.; Pauls, H. W.; Liang, D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1241. (g) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825. (h) Lipshutz, B. H. *Synthesis* **1987**, 325.

(10) Prepared in three steps from glutaryl dichloride according to the following sequence: (a) Br, 90 °C, *hv*, (b) LAH/AlCl₃, Et₂O (94% yield two steps), and (c) KOH, Et₂O (96%).

(11) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043.

(12) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

the *syn* tetraol derivative **7** with excellent stereoselectivity. The double 1,2-Wittig rearrangement of **8** provided **9** in low yield but with the expected *syn* selectivity.^{11,14}

In order to differentiate the vinyl groups present in **4**, a chiral, nonracemic reagent or catalyst must be employed. As in the earlier study, we have examined the Sharpless asymmetric epoxidation reaction for this purpose.² Like the simple divinyl carbinols, **4** undergoes epoxidation with group and face selectivity with the *pro-S* and *pro-R* selective Sharpless reagents to provide either **10**¹⁵ ($[\alpha]_D^{25} -0.86^\circ$, c 1.51, CHCl_3) or **11** ($[\alpha]_D^{25} +0.80^\circ$, c 1.50, CHCl_3), respectively. The minor enantiomers produced in these reactions are selectively "destroyed" by a fast second epoxidation reaction (kinetic resolution). Accordingly, the enantiomeric excess increases as the reaction proceeds to completion; with substrates such as **4**, **9**, and **12** we expect extremely high levels of enantiomeric purity to be obtained ($ee > 99.99999$).² The *pro-S* selective reagent converts **12**¹⁶ into **13** and **9** into **14** in excellent yield and enantioselectivity. It is interesting to note that the reaction determines the absolute stereochemistry at six and seven stereocenters in **13** and **14**, respectively. Since both Sharpless reagents are available, advanced meso synthetic intermediates such as **9** can now be converted into either of two antipodal products.

Compound **14** has been converted to the all *syn* hexaol derivative **15** by the transformations depicted in Scheme IV. On comparison with the degradation product **1**, it is clear that these substances have an *isomeric* relationship. Consequently, we conclude that mycoticin A does not contain the all *syn* polyol configuration.¹⁷ It is apparent that the assumptions concerning the common biogenesis of members of this class require reevaluation.

In summary, enantiotopic group selective reactions are capable of converting achiral, meso compounds into either of two antipodal products and with enhanced levels of enantiomeric purity.¹⁸ These reactions provide a solution to the problem of terminus differentiation presented by the two-directional synthesis strategy that utilizes achiral (class A)¹ chains.¹⁹ The present illustration resulted in the enantioselective formation of *syn*-skipped polyol chains. A report on further investigations concerning the stereochemistry of mycoticin A will be forthcoming.

Acknowledgment. These investigations were supported by the NIH, NSF (Presidential Young Investigator Award), Alfred P. Sloan Foundation (1985-87), and The Camille and Henry Dreyfus Foundation, Inc. (Teacher/Scholar Award 1984-89) to whom we are grateful. Matching funds for the NSF/PYI Award were generously provided by Berlex Co., Stuart Pharmaceuticals, and Pfizer, Inc. We thank Zhaoyin Wang for stimulating discussions that helped catalyze these investigations.

Supplementary Material Available: X-ray crystallographic and spectral data and degradation scheme (25 pages). Ordering information is given on any current masthead page.

(13) (a) Muxfeldt, H.; Haas, G.; Hardtmann, G.; Kathawala, F.; Moberry, J. B.; Vedejs, E. *J. Am. Chem. Soc.* **1979**, *101*, 689. (b) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686.

(14) The low yields associated with the 1,2-Wittig rearrangement make this reaction unattractive in a preparative sense. In the present study, the application of this transformation in two directions provided ready access to sufficient quantities of materials to allow for structural comparison with naturally derived substances. In theory, any synthesis of *syn* 1,3-diols that relies solely on internal asymmetric induction can be conducted simultaneously in two directions.

(15) The stereochemistry of **10** was supported by the X-ray crystallographic structure determination of the corresponding bisacetate. Details are available in the Supplementary Material.

(16) Prepared from **4** according to the sequence: (a) TBSCl, imidazole, CH_2Cl_2 (94%); (b) i. O_3 , CH_2Cl_2 ; ii. $(\text{Ph})_3\text{P}$, room temperature, iii. triethyl phosphonoacetate, NaH , 0°C (80%); (c) DIBAL, CH_2Cl_2 (91%); (d) BnBr , NaH , DMF (90%); (e) tetrabutylammonium fluoride, THF (96%).

(17) The *anti* relationship depicted between the C_2 methyl and C_3 oxygen substituents of **1** has been established from degradation studies of mycoticin A (unpublished results).

(18) For an example of terminus differentiation of a meso chain, see: Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronska, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501.

(19) An early application of the two-directional strategy suffered only at this late stage task, see: Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

Reductive Elimination Pathways to Low-Valent Titanium Aryloxy Complexes

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The lower valent compounds of titanium have been associated with a wide range of inorganic and organometallic reactivity.² In particular the reduction of titanium alkoxides³ and phenoxides⁴ has been reported to lead to a number of very reactive but difficult to characterize titanium(II) derivatives, some of which have the ability to coordinate and activate dinitrogen.³⁻⁵ However, to date there has been no report of a well-characterized titanium(II) alkoxide or phenoxide in the literature. We wish to report here the generation of a number of Ti(II) and Ti(III) aryloxy compounds by ligand induced reductive-elimination pathways from a Ti(IV) organometallic compound.⁶

The mono- η^2 -iminoacyl compound $\text{Ti}(\text{OAr}-2,6\text{-}i\text{-Pr}_2)_2(\eta^2\text{-}t\text{-BuNCCH}_2\text{Ph})(\text{CH}_2\text{Ph})$ (**1**)⁷ will react smoothly over a period of hours with pyridine (≥ 1 equiv) in hydrocarbon solvents to produce the η^2 -imine compound $\text{Ti}(\text{OAr}-2,6\text{-}i\text{-Pr}_2)_2\eta^2\text{-}t\text{-BuNC}(\text{CH}_2\text{Ph})_2(\text{py})$ (**2a**) (Scheme I).⁸ A single-crystal X-ray diffraction study of the 4-phenylpyridine derivative (**2b**)⁹ confirmed

(1) Camille and Henry Dreyfus Teacher-Scholar, 1985-1990 and Fellow of the Alfred P. Sloan Foundation, 1986-1990.

(2) (a) *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A., Eds.; Pergamon Press: Oxford, 1982; Vol. 3, Chapter 22.2 and references therein. (b) Wailes, P. C.; Coultis, R. S. P.; Weigold, H., *Organometallic Chemistry of Titanium, Zirconium and Hafnium*; Academic Press: New York, 1974.

(3) Van Tamelen, E. E. *Acc. Chem. Rev.* **1970**, *3*, 361 and references therein.

(4) Flamini, A.; Cole-Hamilton, D. J.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1978**, 454.

(5) See, also: Sanner, R. D.; Duggon, D. M.; McKenzie, T. C.; Marsh, R. E.; Bercaw, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 8358 and references therein.

(6) Carbonylation of titanocene dialkyls has been shown to lead to $\text{Cp}_2\text{Ti}(\text{CO})_2$ with the elimination of ketones, via $\eta^2\text{-R}_2\text{CO}$ complexes which can sometimes be isolated, see: (a) Erker, G.; Dorf, U.; Czisch, P.; Petersen, J. L. *Organometallics* **1986**, *5*, 668 and references therein. (b) Fachinetti, G.; Floriani, C. *J. Am. Chem. Soc.* **1961**, *83*, 1287. (c) Demerseman, L. B.; Bouquet, G.; Bigorgne, M. *J. Organomet. Chem.* **1977**, *132*, 223.

(7) Chamberlain, L. R.; Durfee, L. D.; Fanwick, P. E.; Kobriger, L.; Latesky, S. L.; McMullen, A. K.; Rothwell, I. P.; Folting, K.; Huffman, J. C.; Strieb, W. E.; Wang, R. *J. Am. Chem. Soc.* **1987**, *109*, 390.

(8) Addition of pyridine (py , ≥ 1 equiv) to a solution of $\text{Ti}(\text{OAr}-2,6\text{-}i\text{-Pr}_2)_2(\eta^2\text{-}t\text{-BuNCCH}_2\text{Ph})(\text{CH}_2\text{Ph})$ (1.9 g, 2.8 mmol) in benzene (30 mL) results in the formation of **2a** over 90 min. Removal of benzene solvent in vacuo followed by addition of hexane gave the product as a red-brown solid in essentially quantitative yield. The 4-phenylpyridine derivative **2b** was obtained via an identical procedure, and X-ray quality crystals were obtained from hexane on slow cooling. Anal. Calcd for $\text{TiC}_{45}\text{H}_{62}\text{N}_2\text{O}_2$ (**2a**): C, 77.18; H, 8.37; N, 3.75. Found: C, 75.92; H, 8.48; N, 3.40. Anal. Calcd for $\text{TiC}_{54}\text{H}_{66}\text{O}_2\text{N}_2$ (**2b**): C, 78.80; H, 8.08; N, 3.40. Found: C, 79.52; H, 8.41; N, 3.51. Selected spectroscopic data: $^1\text{H NMR}$ (C_6D_6 , 30°C) (**2a**) δ 3.63 (d), 3.77 (d, CH_2Ph), 1.30 (s, CMe_3), 3.73 (septet, CHMe_2), 1.16 (d), 1.19 (d, CHMe_2), (**2b**) δ 3.83 (d), 3.95 (d, CH_2Ph), 1.44 (s, CMe_3), 3.88 (septet CHMe_2), 1.28 (d), 1.35 (d, CHMe_2). $^{13}\text{C NMR}$ (C_6D_6 , 30°C) (**2a**) δ 95.0 (NC), 47.0 (CH_2Ph), 64.1 (CMe_3), 32.5 (CMe_3), (**2b**) δ 96.8 (NC), 47.2 (CH_2Ph), 64.2 (CMe_3), 32.6 (CMe_3).

(9) Crystal data for $\text{TiO}_2\text{N}_2\text{C}_{54}\text{H}_{66}$ (**2b**) at -155°C : space group $P2_1/c$, $a = 12.970$ (4) Å, $b = 12.927$ (3) Å, $c = 28.140$ (4) Å, $\beta = 97.38$ (2)°, $Z = 4$, $d_{\text{calcd}} = 1.168$ g cm^{-3} . Of the 6427 unique data collected by using $\text{Cu K}\alpha$ radiation, $3^\circ \leq 2\theta \leq 112^\circ$, the 3514 with $F > 3\sigma(F)$ were used in the final refinement. Final residuals are $R = 0.051$, $R_w = 0.068$.