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Stereoselective syntheses of unnatural steroidal C(20*R*) aldehydes by ionic hydrogenation of C-20 tertiary alcohols

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Abstract—Syntheses of three unnatural steroidal C(20*R*) aldehydes have been realised from 16-dehydropregnenolone acetate. The salient feature of the synthesis is the ionic hydrogenation of C-20 tertiary alcohols leading to the formation of the C(20*R*) unnatural isomer with complete stereoselectivity. Oxidative hydrolysis of the dithiane moiety furnished the C(20*R*) aldehydes.

Steroidal C-20 aldehydes are useful intermediates for the synthesis of a variety of biologically active steroids such as brassinosteroids,[1a] squalamine,[1b] vitamin D_3,[1c,d] OSW-1[1e] ecdysones[1f] and sterols.[2] Compounds with unnatural configuration at C-20 such as isocholesterol **1**, with C(20*S*) stereochemistry showed a significant in vitro inhibitory activity for the conversion of cholesterol to pregnenolone.[3] In addition, 20-*epi* vitamin D_3 **2a**,[4] 20-*epi* cholanic acid derivatives **4a**–**d**[5] and other 20-*epi* steroids[6] have attracted attention because of the interesting biological activities of these epimers and hence the methods for their stereoselective synthesis are highly desirable (Fig. 1). Recently, it was reported[4,7] that the 20-*epi* analogue of the metabolite of vitamin D_3, **2a** is more potent in regulating cell growth and differentiation than the corresponding natural C-20 stereoisomer **2b**. It is also interesting that the 20-*epi* analogue **2a** exhibits immunosuppressive properties[8] and that the 1α-fluoro-16,23-diene-20-*epi* hybrid deltanoid (Ro 26-9228) **3** is in human clinical trials for the treatment of osteoporosis.[9]

Several reports on the construction of the steroidal side chain with unnatural configuration at C-20 using difficult to access reagents and specialised conditions are available.[10] These 20-*epi* isomers have been prepared[5,11,12] from unnatural steroidal C(20*R*) aldehydes **5**–**8** (Fig. 2), which in turn were obtained by epimerisation[5,11,12] of the corresponding C(20*S*) aldehydes and acid catalysed rearrangement[13] of C-20,22-oxido steroids. However, the yields of these aldehydes following these methods are typically poor. Therefore, it was desirable to explore and establish an efficient route for the stereoselective synthesis of steroidal C(20*R*) aldehydes.

Recently, we reported[14] the synthesis of C(20*R*) aldehydes **5** (in five steps with an overall yield of 65%) and **6** (in eight steps with an overall yield of 27%) from a common intermediate **10** by the ionic hydrogenation of the C-20,22-ketene dithioacetal with a 100% stereoselectivity. In continuation of this work,[14] we report here the stereoselective synthesis of aldehydes **5** and **6** by deoxygenation of steroidal C-20 tertiary alcohols **10**–**12** with 100% C(20*R*) stereoselectivity (Scheme 1). This method involves fewer steps from the same intermediate **10** and leads to excellent overall yields (aldehyde **5** in four steps with an overall yield of 81% and aldehyde **6** in four steps with an overall yield of 38%). Stereoselective synthesis of the unknown C-5(6)-saturated C(20*R*) aldehyde **22** by deoxygenation of the C-20 tertiary alcohol group of compound **20** is also reported here (Scheme 2). Aldehyde **22** is an excellent starting material for the synthesis of a variety of C-5 saturated[5] C-20-*epi* steroid side chain compounds. Taking full advantage of the ionic hydrogenation of tertiary alcohols, generation of the C(20*R*) stereocentre

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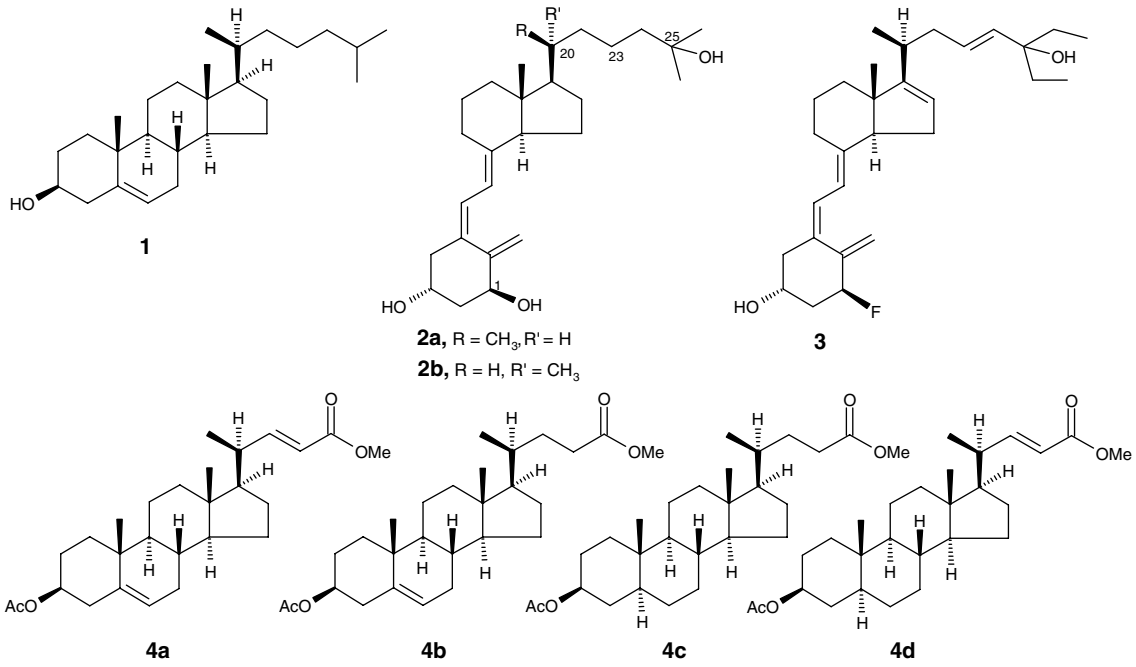


Figure 1. Isocholesterol **1**, vitamin D_3 **2**, deltanoid (Ro 26-9228) **3** and 20(*S*) cholanic acid derivatives **4a**–**d**.

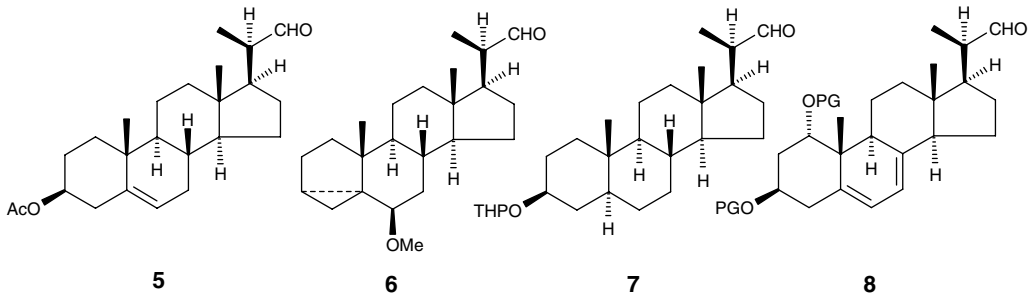


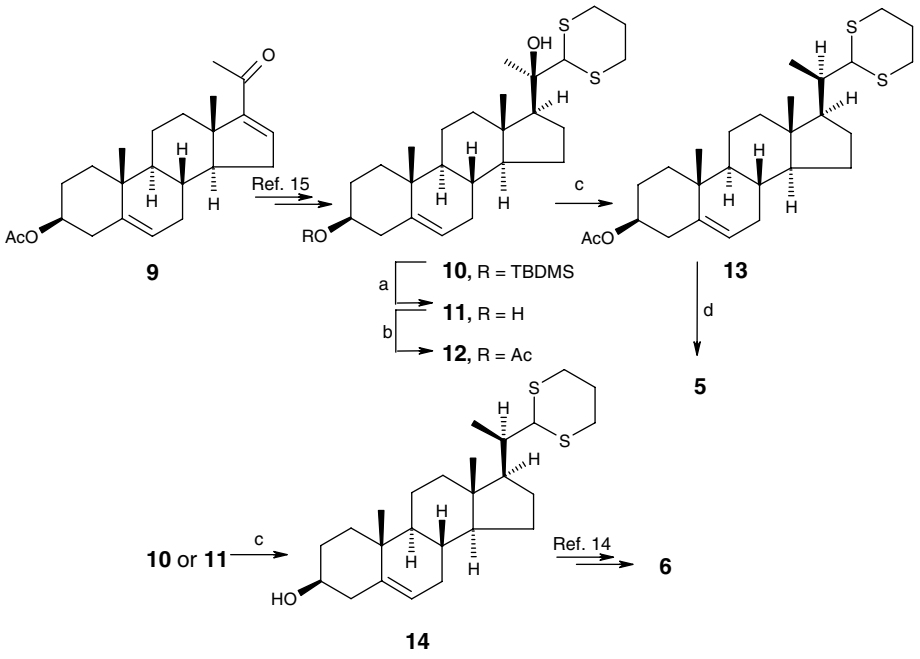
Figure 2. Steroidal C(20*R*) aldehydes **5**–**8**.

leading to the formation of steroidal C(20*R*) aldehydes **5**, **6** and **22** has been carried out successfully and is documented here.

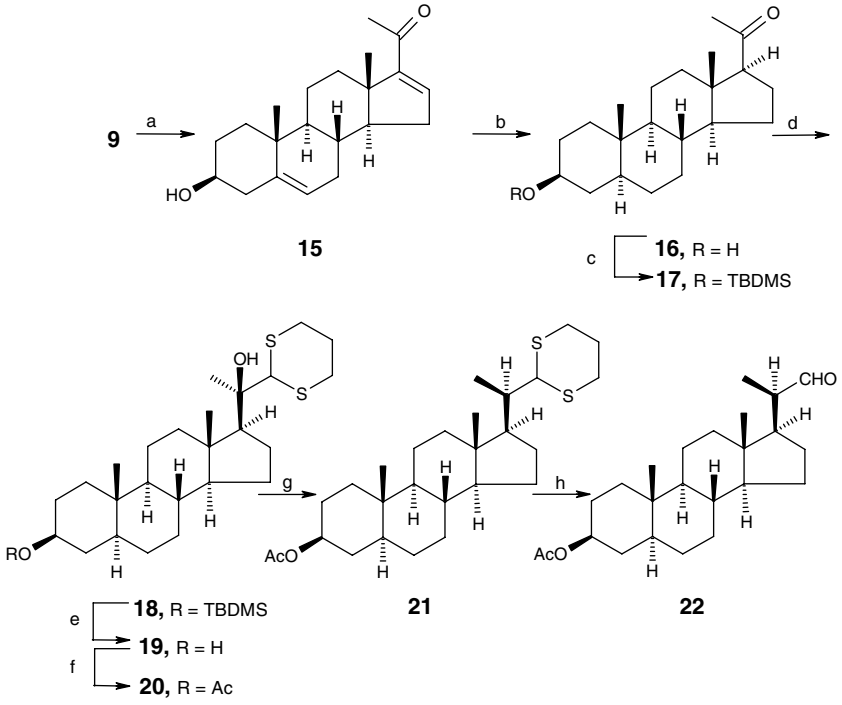
Commercially available 16-dehydropregnenolone acetate **9** was converted[15a] into its C(20*R*) *tert*-alcohol **10** in four steps with a 71% overall yield (Scheme 1). The 3-*tert*-butyldimethylsilyl group of compound **10** was deprotected with *n*-Bu_4NF in tetrahydrofuran followed by the selective acetylation of the secondary alcohol of diol **11** to afford acetate **12** in an 89% yield in two steps.

Ionic hydrogenation is an effective method for the removal of tertiary alcohols[16] and there are several reports on the deoxygenation of steroidal alcohols. Palladium-catalysed hydrogenolysis of steroidal C-20 tertiary allylic carbonates,[17a] radical deoxygenation[17b] of steroidal tertiary alcohols via trifluoroacetates using diphenylsilane/di-*tert*-butylperoxide, radical deoxygenation of steroidal C-11 tertiary oxalates,[17c] deoxygenation of (20*R*)-20-hydroxy-20-isoxazolinyl steroids to isosteroidal side chains by trifluoroacetic acid in refluxing nitromethane in the presence of lithium perchlorate[17d] and ionic hydrogenation with triethylsilane for the stereoselective reduction of hydroxylated estradiol derivatives[18] have been well documented. On the basis of these findings, we envisaged that C-20 tertiary alcohol **10** on ionic hydrogenation would lead to the C-20 deoxygenated product in a single step instead of two steps[14] (dehydration followed by ionic hydrogenation). It would also be of interest to determine the extent of stereospecificity on deoxygenation of the C-20 tertiary alcohol.

The attempted ionic hydrogenation of C-20 *tert*-alcohol **12** using triethylsilane and trifluoroacetic acid in dichloromethane[19] at 34 °C for 2 h furnished deoxygenated product **13** having the C(20*R*) stereochemistry in a low yield (41%). When the same reaction was carried out using Et_3SiH and borontrifluoride–diethyl etherate ($BF_3{\cdot}OEt_2$) at 0 °C for 10 min, the C-20 deoxygenated product **13** was obtained in an excellent yield (94%) (Scheme 1). Compound **10**, on exposure to similar reaction conditions (Et_3SiH, $BF_3{\cdot}OEt_2$), led to deoxygenation of the C-20 *tert*-alcohol along with deprotection of the TBDMS group to give compound **14** in a 90% yield. Under identical reaction conditions, the 3,20-diol



Scheme 1. Reagents and conditions: (a) *n*-Bu_4NF (2 equiv), THF, 30 °C, 18 h, 93%; (b) Ac_2O (2 equiv), pyridine, DMAP (0.2 equiv), 25 °C, 2 h, 96%; (c) Et_3SiH (6 equiv), $BF_3{\cdot}OEt_2$ (10 equiv), DCM, 0 °C, 10 min, 90–94%; (d) HgO (1.25 equiv), $HgCl_2$ (2 equiv), CH_3CN, H_2O, reflux, 3 h, 96%.



Scheme 2. Reagents and conditions: (a) KOH (5 equiv), *t*-BuOH, H_2O, 30 °C, 10 h, 96%; (b) 10% Pd/C, H_2, EtOH, 55 psi, 30 °C, 12 h, 99%; (c) TBDMSCl (1.25 equiv), imidazole (1.5 equiv), DMF, 30 °C, 10 h, 97%; (d) 1,3-dithiane (1.5 equiv), *n*-BuLi (1.8 equiv), THF, −30 °C for 2 h and 0 °C for 12 h, 82%; (e) *n*-Bu_4NF (2 equiv), THF, 30 °C, 18 h, 93%; (f) Ac_2O (2 equiv), pyridine, DMAP (0.2 equiv), 25 °C, 2 h, 97%; (g) Et_3SiH (6 equiv), $BF_3{\cdot}OEt_2$ (10 equiv), DCM, 0 °C, 10 min, 94%; (h) HgO (1.25 equiv), $HgCl_2$ (2 equiv), CH_3CN, H_2O, reflux, 3 h, 96%.

11 furnished the same product **14** in an excellent yield (92%). It is worth mentioning that varying the temperature (−35 to 30 °C) for the ionic hydrogenation of **12** gave the same product and yield with small differences in the reaction time (30 min to 5 min). The physical and spectroscopic data of compounds **13** and **14** were found to be identical in all respect with the compounds synthesised earlier[14] by the ionic hydrogenation of the C-20,22-ketene dithioacetal. We have carried out the X-ray crystallographic analysis of compound **13** and

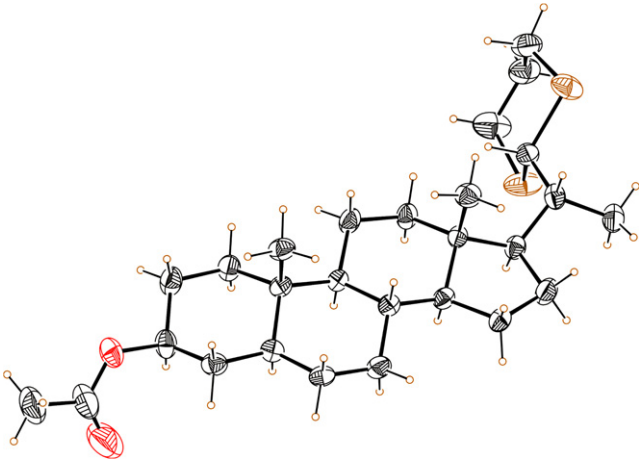


Figure 3. ORTEP view of 3β-acetoxy-5α-pregna-20(*R*)-20-dithiane **21**.

found it to be identical with that reported.[14] Following a known procedure,[14] intermediates **13** and **14** have been elaborated to C(20*R*) aldehydes **5** and **6**.

After the successful synthesis of steroidal C(20*R*) aldehydes **5** and **6**, our next goal was to synthesise C-5(6)-saturated aldehyde **22**. Hydrolysis of the acetate functionality of 16-dehydropregnenolone acetate **9** with KOH in *t*-butanol followed by the catalytic hydrogenation of **15** in ethanol with 10% Pd/C afforded 5α-pregnane-3β-ol-20-one **16** in a 95% yield in two steps (Scheme 2). It is interesting to note that the catalytic hydrogenation of compound **15** with 10% Pd/C in ethyl acetate[15] only reduced the 16(17)-double bond, while in ethanol both the 5(6) and 16(17)-double bonds were reduced. A general trend that could be termed 'solvent effect' is emerging from these hydrogenation experiments.

The 3β-OH group of **16** was transformed to its TBDMS derivative **17**[20] in an excellent yield (97%). The exposure of compound **17** to 2-lithio-1,3-dithiane and deprotection of the TBDMS group of **18**[21] with *n*-Bu_4NF yielded 3,20-diol **19** in a 76% yield over two steps. Selective acetylation of the 3-hydroxy group of compound **19** furnished acetate **20** in a 97% yield. Compound **20** on ionic hydrogenation with triethylsilane and borontrifluoride–diethyl etherate in dichloromethane at 0 °C afforded compound **21** in an excellent yield (94%).

The unnatural C(20*R*) configuration in compound **21** was assigned by physical and spectroscopic data[22] and confirmed unambiguously by single crystal X-ray analysis[23] (Fig. 3).

Regarding the stereochemical outcome of deoxygenation of C-20 *tert*-alcohols **10**–**12** and **20** by ionic hydrogenation, it can be anticipated that there may be a 1,2-hydride shift from C-22 of dithiane moiety of intermediate **A** leading to sulfur stabilised carbocation **B**. Hydride transfer from triethylsilane to C-22 leads to the formation of compound **C** (Fig. 4). During deoxygenation of the C-20 tertiary alcohol, a 1,2-hydride shift from the less hindered α-face determines the stereochemical outcome of the product. On the other hand, ionic

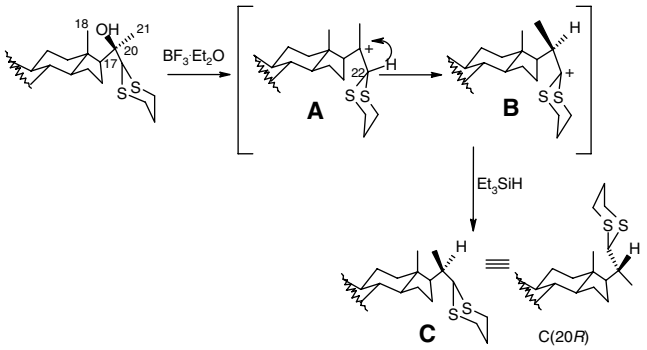


Figure 4. Proposed mechanism for the deoxygenation of *tert*-alcohols.

hydrogenation[14] of a C-20,22-ketene dithioacetal to a C-20,22-dihydro product is governed by protonation with trifluoroacetic acid at C-20 leading to the observed stereochemical outcome. Thus, ionic hydrogenation of a C-20,22-ketene dithioacetal and also ionic hydrogenation of C-20 *tert*-alcohols, both lead to the generation of the C(20*R*) unnatural configuration with 100% selectivity.

Removal of the C-20-dithiane moiety by the oxidative hydrolysis of compound **21** with HgO–$HgCl_2$ yielded C(20*R*) aldehyde **22** in a 96% yield. This is the first report of the stereoselective synthesis of C(20*R*) aldehyde **22** with a 100% selectivity from 16-dehydropregnenolone acetate **9**.

In summary, steroidal C-20 *tert*-alcohols were obtained from 16-dehydropregnenolone acetate in an excellent overall yield. Ionic hydrogenation of the *tert*-alcohols with Et_3SiH–$BF_3{\cdot}OEt_2$ led to the C(20*R*) unnatural configuration with a 100% selectivity, which was confirmed unambiguously by X-ray crystallographic analysis. Utilisation of these unnatural C(20*R*) aldehydes to elaborate the side chain of a large variety of highly potent naturally occurring 20-*epi* steroids is in progress.

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21. Compound **18**: crystalline solid; $[\alpha]_D^{24}$ −17.39 (*c* 0.57, $CHCl_3$). IR (Nujol, cm^{-1}) 3388 (OH). ^1H NMR (200 MHz, $CDCl_3$) $\delta = 4.14$ (s, 1H, 22-H), 3.52 (m, 1H, 3-H), 2.90 (m, 4H, dithiane-CH_2), 1.42 (s, 3H, 21-H_3), 0.88 (s, 9H, $SiCMe_3$), 0.85 (s, 3H, 19-H_3), 0.79 (s, 3H, 18-H_3), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 78.02$ (C), 72.38 (CH), 61.48 (CH), 56.84 (CH), 55.45 (CH), 54.57 (CH), 45.22 (CH), 43.48 (C), 40.66 (CH_2), 38.90 (CH_2), 37.41 (CH_2), 35.70 (C), 35.12 (CH), 32.20 ($2 \times CH_2$), 31.78 (CH_2), 31.09 (CH_2), 29.01 (CH_2), 26.30 (CH_2), 26.22 ($3 \times CH_3$), 24.37 (CH_3), 23.92 (CH_2), 21.90 (CH_2), 21.37 (CH_2), 18.50 (C), 13.85 (CH_3), 12.63 (CH_3), −4.28 ($2 \times CH_3$). Anal. Calcd for $C_{31}H_{56}O_2SiS_2$: C, 67.33; H, 10.20; S, 11.59. Found: C, 67.22; H, 9.96; S, 11.33.
22. Compound **21**: crystalline solid; $[\alpha]_D^{24}$ +11.82 (*c* 1.01, $CHCl_3$). IR (Nujol, cm^{-1}) 1730 ($OCOCH_3$). ^1H NMR (200 MHz, $CDCl_3$) $\delta = 4.68$ (m, 1H, 3-H), 4.37 (d, $J = 2.0$ Hz, 1H, 22-H), 2.84 (m, 4H, dithiane-CH_2), 2.02 (s, 3H, $OCOCH_3$), 1.06 (d, 3H, $J = 6$ Hz, 21-H_3), 0.82 (s, 3H, 19-H_3), 0.67 (s, 3H, 18-H_3). ^{13}C NMR ($CDCl_3$, 50 MHz) $\delta = 170.48$ (C), 73.58 (CH), 55.85 (CH), 55.39 (CH), 54.11 (CH), 51.91 (CH), 44.51 (CH), 42.66 (C), 40.38 (CH), 38.96 (CH_2), 36.64 (CH_2), 35.35 (C), 35.35 (CH), 33.89 (CH_2), 31.78 (CH_2), 31.61 (CH_2), 30.53 (CH_2), 28.45 (CH_2), 27.36 (CH_2), 27.20 (CH_2), 26.34 (CH_2), 23.89 (CH_2), 21.33 (CH_3), 21.15 (CH_2), 15.87 (CH_3), 12.22 (CH_3), 12.12 (CH_3). MS (LCMS) *m*/*z*: 464 (M^+). Anal. Calcd for $C_{27}H_{44}O_2S_2$: C, 69.77; H, 9.54; S, 13.79. Found: C, 69.87; H, 9.52; S, 13.74.
23. *Crystallographic data for* **21** ($C_{27}H_{44}O_2S_2$): $M = 464.74$, crystal dimensions $0.61 \times 0.43 \times 0.03$ mm^3, monoclinic, space group $P2_1$, $a = 6.7783(18)$, $b = 6.7783(18)$, $c = 31.048(9)$ Å, $\beta = 95.395(5)°$, $V = 2636.4(12)$ $Å^3$, $Z = 4$; $\rho_{calcd} = 1.171$ g cm^{-3}, μ (Mo-K_α) = 0.223 mm^{-1}, $F(000) = 1016$, $2\theta_{max} = 50.00°$, 19022 reflections collected, 8559 unique, 5706 observed ($I > 2\sigma(I)$) reflections, 567 refined parameters, R value 0.0527, $wR_2 = 0.1124$ (all data $R = 0.0889$, $wR_2 = 0.1243$), $S = 1.015$, minimum and maximum transmission 0.8771 and 0.9945, respectively, maximum and minimum residual electron densities +0.295 and −0.197 e $Å^{-3}$. Crystallographic data (excluding structure factors) for the structure **21** in this letter has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication number CCDC 606459.