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Studies directed towards the synthesis of schisanartane and related complex nortriterpenoids: construction of models of the peripheral ABC and FGH segments of rubrifloradilactone C

Goverdhan Mehta *, Bilal Ahmad Bhat, T. H. Suresha Kumara

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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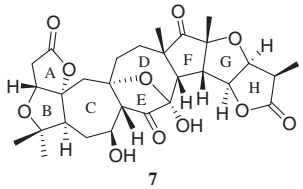
ABSTRACT

A conceptually unifying and flexible approach to the ABC and FGH segments of the nortriterpenoid rubrifloradilactone C, each embodying a furo[3,2-*b*]furanone moiety, from the appropriate Morita–Baylis–Hillman adducts is delineated.

1. Introduction

Few natural product groupings can match the structural complexity and diversity, as well as functional group density, encountered among the recently discovered and rapidly growing family of *Schisandra* nortriterpenoids.[1] An impressive number of nortriterpenoids embodying complex architecture and exhibiting biological activity ranging from anti-HIV to cytotoxic have been isolated and characterized from the Chinese medicinal plants of the *Schisandracea* family.[1] On the basis of the biosynthetic pathways followed, the various skeletal motifs present in *Schisandra* nortriterpenoids have been broadly classified into six main categories comprising of schisanartane (e.g., schirubridilactone A **1**), schiartane (e.g., micrandilactone B **2**), 18-norshiartane (e.g., rubrifloradilactone A **3**), 18(13→14)-*abeo*-shiartane (e.g., wuweizidilactone F **4**), pre-schisanartane (e.g., pre-schisanartanin A **5**) and wuweiziartane (e.g., schintrilactone A **6**), Figure 1.[1l] Each member of this exotic nortriterpenoid family (e.g., **1–6**) constitutes a formidable challenge and an ambitious target for total synthesis endeavors. Therefore, it is not surprising that these *Schisandra* nortriterpenoid natural product targets are beginning to draw widespread attention from the synthetic organic chemistry community.[2] The efforts of the past few years in this arena are still exploratory in nature and probe the feasibility of a particular strategy, and are by and large confined to the model construction of various ring fragments. We too have been enchanted by the complexity of the *Schisandra* nortriterpenoids and their potential bioactivity, and selected rubrifloradilactone C (**7**), a recently reported[1k] member of the schisanartane group from *Schisandra rubriflora*, as a target for our synthetic efforts. In this Letter, we disclose our preliminary results towards the rapid assembly of the prototypical ABC and FGH segments present in the natural product **7**.



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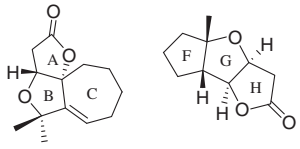

8 **9**

The octacyclic structure of rubrifloradilactone C (**7**), embellished with 14 stereogenic centres and 11 oxygen atoms was deduced through a combination of extensive 2D NMR analysis and computational studies employing DFT methods.[1k] In contemplating a synthetic approach to this formidable ensemble of rings, oxy-functionalities and stereogenicity, we initially embarked on a sectorial approach and focussed on devising a viable methodology for the construction of the two peripheral segments **8** and **9**, constituting the ABC and FGH rings, respectively. In this context, it occurred to us that both the ABC and FGH segments, present in **7**, embody a common furo[3,2-*b*]furanone core (AB and GH rings) which should be readily accessible through our recently delineated[3] bidirectional approach based on Morita–Baylis–Hillman (MBH) adducts, Scheme 1. Thus, an appropriately crafted MBH adduct, for example, **10** could eventuate to either the spiro-fused ABC segment **11** through pathway A or the linearly fused FGH segment **12** following pathway B, Scheme 1.

* Corresponding author. Tel.: +91 8023600367; fax: +91 8023600283.
E-mail address: gm@orgchem.iisc.ernet.in (G. Mehta).

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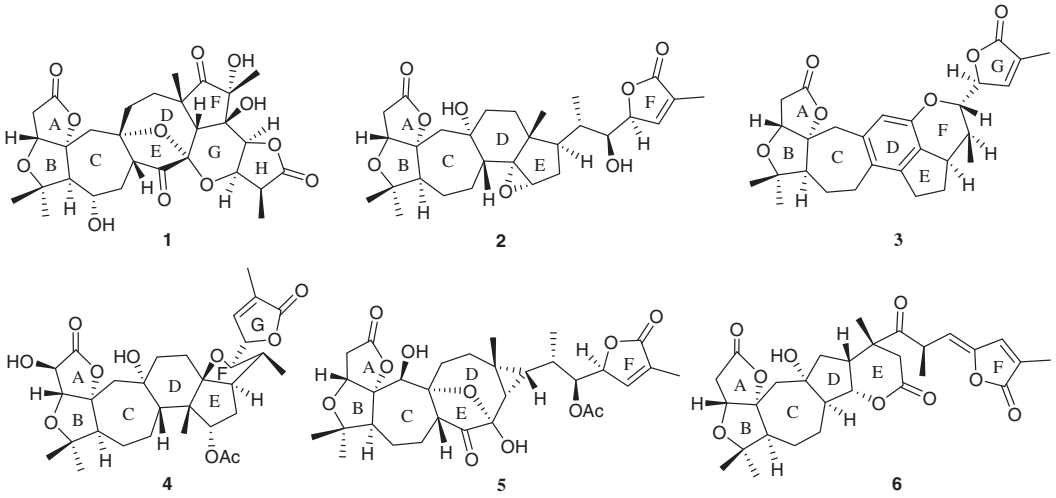
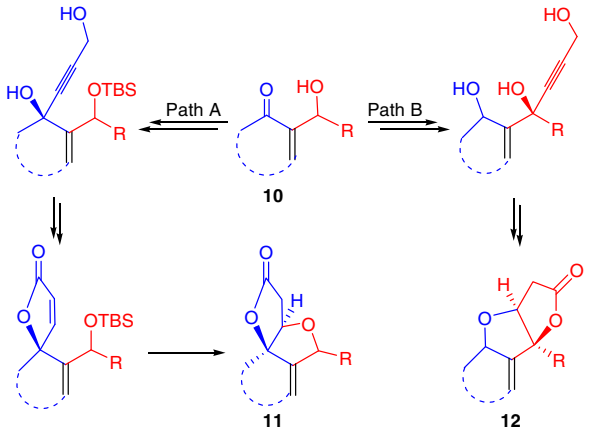


Figure 1. Structural diversity among *Schisandra* nortriterpenoid natural products.

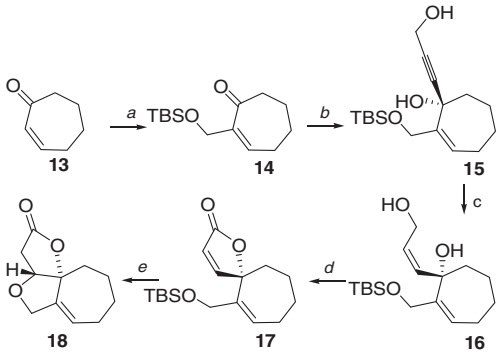


Scheme 1. Adaptation of the MBH adduct-based bidirectional approach to the ABC and FGH segments embodying a furo[3,2-*b*]furanone moiety.

2. Synthesis of the ABC segment

Our initial focus was on the spiro-fused ABC ring system **8**, following path A (**10**→**11**), as this segment is ubiquitous among the *Schisandra* nortriterpenoids (see **1–6**). In our first foray, TBS-protected cycloheptenone-formaldehyde MBH adduct **14** was obtained from cycloheptenone **13** in two steps and in modest yield, Scheme 2.[4] Direct propargylation of **14** with the dianion derived from propargyl alcohol led to **15** which was regio- and stereoselectively hydrogenated to the allylic alcohol **16**. MnO_2 oxidation of **16** delivered the spiro-fused butenolide **17** via an intermediate lactol. Fluoride-mediated desilylation of **17** led to intramolecular oxy-Michael addition and afforded the basic tricyclic scaffold **18**.[4] This route represents a short sequence from commercial cycloheptenone, Scheme 2.

The next task was the adaptation of the above sequence to access the desired *Schisandra* nortriterpenoid scaffold **8**. Towards this end, **14** was smoothly propargylated to give THP-protected **19**, Scheme 3. TBS deprotection and MnO_2 oxidation of **19** furnished the aldehyde **20**. Elaboration of the aldehyde **20** into the methyl ketone **21** was routine and further addition of methyllithium led to the tertiary alcohol **22**, Scheme 3. THP deprotection in **22** and regio- and stereoselective hydrogenation furnished the *Z*-allylic alcohol **23**.[4] MnO_2-mediated oxidation of **23** triggered a cascade of oxidation-cyclization processes that led directly to the targeted tricyclic ABC scaffold **8**[4] involving intramolecular oxy-Michael addition in the intermediate butenolide **24**, as depicted in Scheme 3.

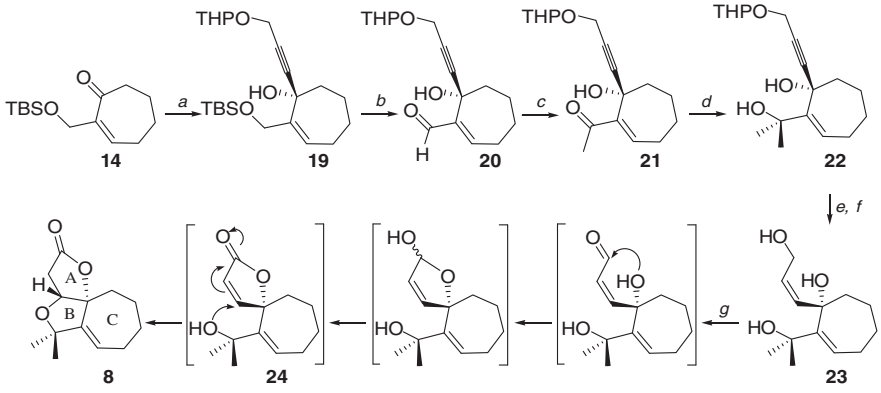


Scheme 2. Reagents and conditions: (a) (i) formalin, DMAP, THF, rt, 6 h; (ii) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 1 h, 46% (over two steps); (b) propargyl alcohol, *n*-BuLi, THF, −78 °C to −20 °C, 6 h, 62%; (c) Lindlar catalyst, H_2, MeOH, rt, 7 h, 92%; (d) MnO_2, CH_2Cl_2, rt, 5 h, 82%; (e) TBAF, THF, rt, 30 min, 95%.

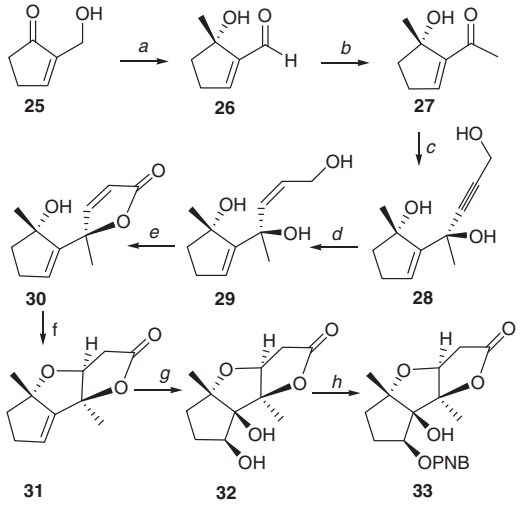
3. Synthesis of the FGH segment

As indicated, for the construction of the FGH segment **9**, an adaptation of pathway B (Scheme 1) had to be devised, and towards this objective, cyclopentenone-formaldehyde MBH adduct **25**[5] was identified as the starting material. Addition of excess methyllithium and MnO_2 oxidation transformed **25** into the aldehyde **26**. Further elaboration of **26** to methylketone **27** was uneventful and set the stage for the propargylation with the dianion of propargyl alcohol to furnish **28** in a stereoselective manner, Scheme 4.

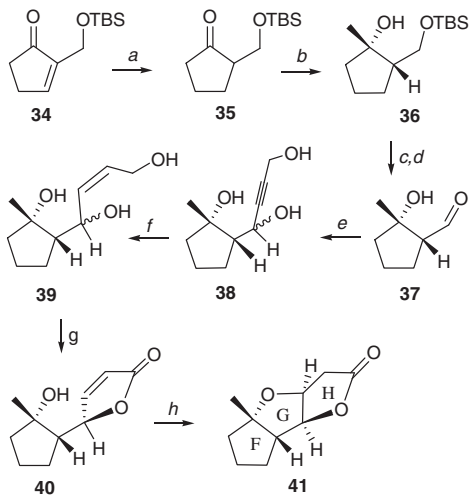
The free tertiary hydroxy group in **27**, quite expectedly facilitated the stereoselective delivery of the propargyl group. Regio- and stereoselective hydrogenation led to the allylic alcohol **29**. Chemoselective oxidation of triol **29** directly delivered the butenolide **30**. DBU activation of **30** resulted in the contemplated intramolecular oxy-Michael addition to deliver the tricyclic furo[3.2-*b*]furanone derivative **31**[4] embodying the FGH segment, Scheme 4. The stereochemistry in **31** was secured by its conversion into the dihydroxy compound **32** through osmylation and X-ray crystal structure[6] determination of its *p*-nitrobenzoate derivative **33**,[4] Scheme 4.



Scheme 3. Reagents and conditions: (a) tetrahydro-2-(propynyloxy)-2*H*-pyran, *n*-BuLi, −70 °C to −20 °C, 8 h, 86%; (b) (i) TBAF, THF, rt, 1 h; (ii) MnO_2, CH_2Cl_2, rt, 2 h, 68% (over two steps); (c) (i) MeLi, THF, 0 °C, 30 min, (ii) MnO_2, rt, 2 h, 52% (over two steps); (d) MeLi, THF, 0 °C, 1 h, 72%; (e) PPTS, EtOH, rt to 55 °C, 56%; (f) Lindlar catalyst, H_2, EtOAc, 1 h, 88%; (g) MnO_2, CH_2Cl_2, rt, 2 h, 92%.



Scheme 4. Reagents and conditions: (a) (i) MeLi, THF, −78 °C, 2 h; (ii) MnO_2, CH_2Cl_2, rt, 4 h, 57% (over two steps); (b) (i) MeLi, THF, −78 °C, 1 h, (ii) MnO_2, CH_2Cl_2, rt, 60% (over two steps); (c) propargyl alcohol, *n*-BuLi, THF, −78 °C to −20 °C, 6 h, 60% (based on recovered starting material); (d) Lindlar catalyst, H_2, EtOAc, 1 h, 85%; (e) MnO_2, CH_2Cl_2, rt, 2 h, 86%; (f) DBU, toluene, reflux, 6 h, 87%; (g) OsO_4, NMMO, acetone/H_2O (4:1), rt to 60 °C, 61%; (h) *p*-nitrobenzoyl chloride, Et_3N, DMAP, rt, 62%.



Scheme 5. Reagents and conditions: (a) Pd/C, H_2, EtOAc, 3 h, rt, 89%; (b) MeMgI, Et_2O, 0 °C, 1 h, 76%; (c) TBAF, THF, rt, 1 h, 80%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 55%; (e) propargyl alcohol, *n*-BuLi, THF, −78 °C to −60 °C, 6 h, 42%; (f) Lindlar catalyst, H_2, EtOAc, 1 h, 83%; (g) TEMPO, CuCl, DMF, rt, 6 h, 36%; (h) DBU, THF, rt, 3 h, 57%.

As an additional example towards the FGH segment, cyclopentenone-derived and TBS-protected MBH adduct **34** was reduced to **35** and methylmagnesium iodide addition led to **36** stereoselectively (4:1), Scheme 5. The TBS group in the major diastereomer **36** was cleaved and the primary hydroxy group oxidized to the aldehyde **37**. Propargylation of **37** was nonstereoselective and furnished a mixture of diastereomers **38** (∼1:1). Stereoselective hydrogenation in **38** led to the allylic alcohols **39**. After considerable experimentation it was found that the primary hydroxy group in **39** could be chemoselectively oxidized to furnish directly the butenolide **40**[4] along with its diastereomer,[7] Scheme 5. Finally, exposure of **40** to DBU resulted in the anticipated intramolecular oxy-Michael addition to furnish **41**[4] whose tricyclic stereostructure corresponding to the FGH segment of **7** was secured on the basis of 2D NMR analysis.

In conclusion, a general approach to the ABC and FGH tricyclic motifs, present in the complex *Schisandra* nortriterpenoid rubriflordilactone C (**7**), with potential for adaptation to other schisanartanes has been devised from the readily available Morita–Baylis–Hillman adducts. Efforts are currently underway to integrate this conceptually unifying approach to the two peripheral wings (ABC and FGH) of the natural product **7** on an appropriately crafted eight-membered D ring platform. These endeavors will be disclosed shortly.

Acknowledgements

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4. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds: **18** IR (neat) 2924, 1770, 1193, 1052, 929 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96–5.91 (m, 1H), 4.55 (d, J = 12 Hz, 1H), 4.38–4.28 (m, 2H), 2.75–2.65 (m, 2H), 2.44–2.32 (m, 1H), 2.25–2.16 (m, 1H), 2.05–1.82 (m, 4H), 1.78–1.72 (m, 1H), 1.55–1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 139.9, 128.0, 93.2, 84.1, 72.1, 35.8, 33.7, 27.6, 27.1, 24.6; HRMS (ES) m/z calcd for $C_{11}H_{14}O_3Na$ (M+Na$^+$): 217.0841; found: 217.0848; **23** IR (neat) 3339, 2927, 1622, 1164, 1017 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81–5.63 (m, 3H), 4.37 (dd, J = 14 Hz, 7 Hz, 1H), 4.24 (dd, J = 14 Hz, 6 Hz, 1H), 2.35–1.97 (m, 6H), 1.75–1.56 (m, 2H), 1.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.4, 124.7, 80.5, 77.2, 58.9, 41.5, 32.2, 31.9, 26.4, 25.7, 24.2, 22.6; HRMS (ES) m/z calcd for $C_{13}H_{22}O_3Na$ (M+Na$^+$): 249.1467; found: 249.1458; **8** IR (neat) 2927, 2360, 1774, 1540, 1178, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, J = 8 Hz, 4 Hz, 1H), 4.28 (d, J = 4 Hz, 1H), 2.75 (dd, J = 18 Hz, 5 Hz, 1H), 2.65 (d, J = 18 Hz, 1H), 2.44–2.33 (m, 1H), 2.25–2.16 (m, 1H), 2.00–1.82 (m, 4H), 1.73–1.66 (m, 1H), 1.57 (s, 3H), 1.47–1.42 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 148.4, 128.2, 94.6, 84.4, 79.7, 77.2, 35.9, 34.7, 28.5, 27.5, 27.2, 24.8; HRMS (ES) m/z calcd for $C_{13}H_{18}O_3Na$ (M+Na$^+$): 245.1154; found: 245.1146; **31** IR (neat) 2926, 1781, 1032, 932 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, J = 4 Hz, 2 Hz, 1H), 4.51 (d, J = 6 Hz, 1H), 2.83 (dd, J =18 Hz, 6 Hz, 1H), 2.73 (d, J = 18 Hz, 1H), 2.70–2.66 (m, 1H), 2.54–2.49 (m, 1H), 2.06–2.03 (m, 2H), 1.59 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 150.5, 128.4, 94.9, 86.2, 85.9, 43.9, 37.8, 34.2, 24.7, 19.5; HRMS (ES) m/z calcd for $C_{11}H_{14}O_3Na$ (M+Na$^+$): 217.0841; found: 217.0841; **33** mp 176–177 °C; IR (neat) 3458, 2925, 1748, 1261, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8 Hz, 2H), 8.24 (d, J = 8 Hz, 2H), 5.41–5.38 (m, 1H), 4.44 (d, J = 4 Hz, 1H), 2.82 (dd, J = 18 Hz, 4 Hz, 1H), 2.74 (d, J = 18 Hz, 1H), 2.68 (br s, 1H), 2.23–2.13 (m, 1H), 2.07–1.96 (m, 3H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 164.1, 150.8, 135.1, 130.9, 123.7, 93.3, 91.1, 87.9, 79.8, 76.6, 38.1, 37.0, 28.8, 23.3, 17.2; HRMS (ES) m/z calcd for $C_{18}H_{19}NO_8Na$ (M+Na$^+$): 400.1008; found: 400.1012; **40** IR (neat) 3447, 2925, 1745, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 6 Hz, 2 Hz, 1H), 6.12 (dd, J = 6 Hz, 2 Hz, 1H), 5.32–5.30 (m, 1H), 1.95–1.87 (m, 1H), 1.78–1.73 (m, 3H), 1.65–1.53 (m, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 156.7, 121.3, 83.3, 79.6, 51.2, 42.8, 28.1, 25.6, 21.8; HRMS (ES) m/z calcd for $C_{10}H_{14}O_3Na$ (M+Na$^+$): 205.0841; found: 205.0836; **41** IR (neat) 3397, 2927, 1785, 1018 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (s, 2H), 2.69–2.62 (m, 3H), 2.02–1.86 (m, 2H), 1.68–1.47 (m, 4H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 95.2, 91.7, 79.0, 53.2, 41.4, 37.8, 29.9, 26.7, 25.4; HRMS (ES) m/z calcd for $C_{10}H_{14}O_3$ (M+Na$^+$): 205.0841; found: 205.0831.

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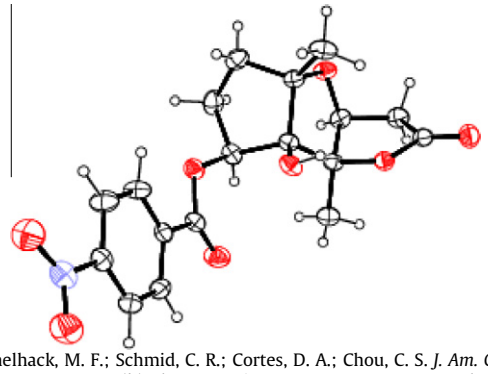
6. X-ray data were collected at 291 K on a Bruker SMART APEX diffractometer with graphite monochromated Mo Kα radiation (λ = 0.7107 Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 using SHELXL-97. The relevant crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. Compound **33**: $C_{18}H_{19}NO_8$, MW = 377.34, crystal system: monoclinic, space group: $P2_1/c$, cell parameters: a = 8.771(2) Å, b = 19.939(5) Å, c = 10.047(2) Å, β = 96.516(5)°, V = 1745.9(7) Å^3, Z = 4, ρ_{calcd} = 1.436 g cm^{-3}, F(0 0 0) = 792, μ = 0.114 mm^{-1}, number of l.s. parameters = 247, $R1$ = 0.0607 for 2050 reflections with $I > 2\sigma(I)$ and 0.1170 for all 3223 data. $wR2$ = 0.1147, GOF = 1.064 for all data, CCDC-764213. An ORTEP diagram of **33**, drawn at 30% ellipsoidal probability, is shown below:



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