Tetrahedron Letters 50 (2009) 3550–3554

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Further studies of an approach to a total synthesis of phomactins

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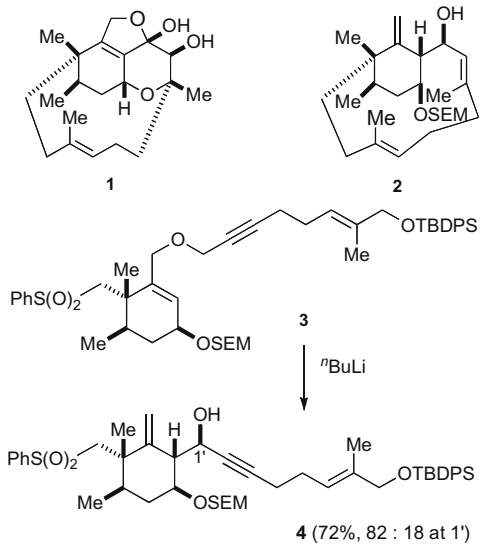
ARTICLE INFO

Article history:
Received 8 January 2009
Revised 3 March 2009
Accepted 5 March 2009
Available online 13 March 2009

ABSTRACT

The bicyclic sulfone **28**, which has the intact carbon skeleton of phomactins, was prepared using a stereoselective [2,3]-Wittig Still rearrangement, a ytterbium triflate-mediated addition of a vinyllithium reagent to an aldehyde and macrocyclisation via an intramolecular sulfone alkylation, as key steps. During studies into the conversion of this intermediate into phomactin A, it was found that oxidation of homoallylic alcohols using TPAP can give unsaturated keto-aldehydes, and the stereoselectivity of reduction of a ketone at C(14) is influenced by the presence of a remote sulfonyl group at C(10).

Phomactin A **1** is the parent member of a group of diterpenes, the phomactins, which are challenging targets for total synthesis, and which possess interesting biological activity including platelet activating factor antagonism.[1] Two total syntheses of phomactin A **1** have been reported to date,[2] together with syntheses of phomactins D,[3] G[4] and B2,[5] and many partial syntheses.[6] The chemistry of the phomactins has been reviewed.[7]



In our work,[8] the monoprotected diol **2** was identified as an advanced intermediate which could be incorporated into syntheses of several members of the phomactin family. It was prepared by a synthesis which involved a stereoselective [2,3]-Wittig rearrangement of the propargylic ether **3** which gave alcohol **4**. However, the conversion of this alcohol into the required intermediate **2** proved difficult to scale up. We now report an improved synthesis of the analogous diol **30** and several unexpected late-stage transformations which were encountered during attempts to complete a synthesis of phomactin A.

It was decided to use the Still variation[9] of the [2,3]-Wittig rearrangement to prepare intermediates for macrocyclisation. A synthesis of the tributylstannanes **17** and **18**, precursors for the Wittig rearrangements, is outlined in Scheme 1. Keto-ester **5**,[8] as a 75:25 mixture of epimers at C(6), was converted into its 2-hydroxymethyl analogue **7** by oxidation of enol ether **6** using methyl(trifluoromethyl)-dioxirane generated in situ.[10] Following silylation of the hydroxyl group, Luche reduction[11] of the enone **8** gave the alcohol **9** as the major product in 65% isolated yield after chromatographic separation from its C(6)-epimer derived from the minor epimer of keto-ester **5**. Following conversion to the *tert*-butyldiphenylsilyl ether **10**, reduction of the methoxycarbonyl group using lithium triethylborohydride gave the alcohol **11** which was converted into thio-ether **13** via mesylate **12**. Selective desilylation then gave the primary alcohol **15** which was alkylated to give the (tributylstannyl)methyl ether **17**. Thio-ether **13** was also oxidised to the sulfone **14** which was taken through to the corresponding (tributylstannyl)methyl ether **18** by O-deprotection and alkylation.

The [2,3]-Wittig rearrangements of the lithiated methyl ethers generated from the sulfide **17** and sulfone **18** were found to proceed with very different stereoselectivities. Thus, on treatment with one equivalent of *n*-butyllithium, sulfide **17** rearranged to give the homoallylic alcohol **20**, in which the hydroxymethyl and

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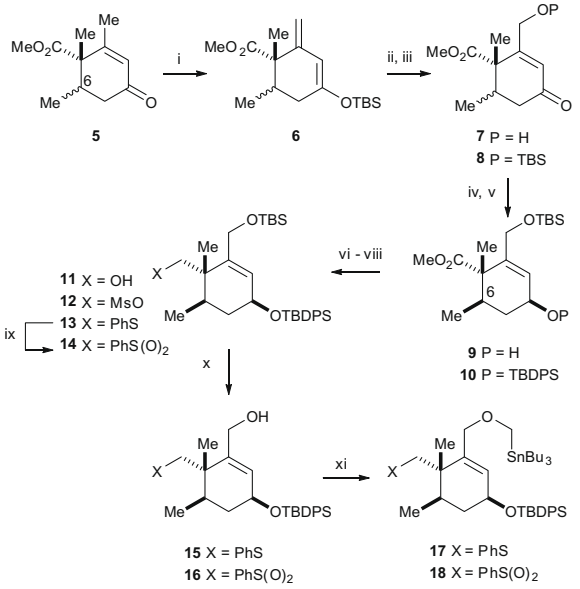
doi:10.1016/j.tetlet.2009.03.042

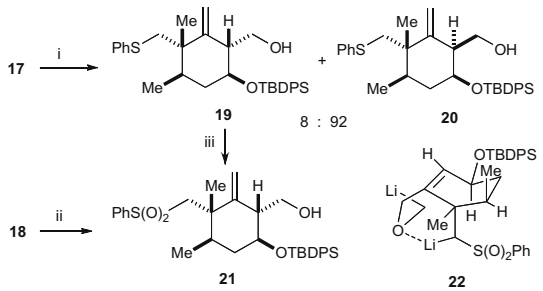


Scheme 1. Reagents and conditions: (i) TBSOTf, Et_3N, DCM, rt (72%); (ii) 1,1,1-trifluoropropanone, Oxone®, $NaHCO_3$, Na_2EDTA, MeCN, H_2O, 0 °C (65%); (iii) TBSCl, imid., DCM, 0 °C to rt (96%); (iv) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C (65%); (v) TBDPSCl, imid., DCM, 0 °C–rt (86%); (vi) $LiEt_3BH$, THF, 0 °C (80%); (vii) MsCl, Et_3N, DCM, 0 °C (95%); (viii) PhSH, NaH, DMF, heat (72%); (ix) ammonium molybdate, H_2O_2, EtOH, 0 °C to rt (88%); (x) HCl, EtOH, rt (**15**, 90%; **16**, 90%); (xi) NaH, Bu_3SnCH_2I, THF, rt (**17**, 82%; **18**, 86%).

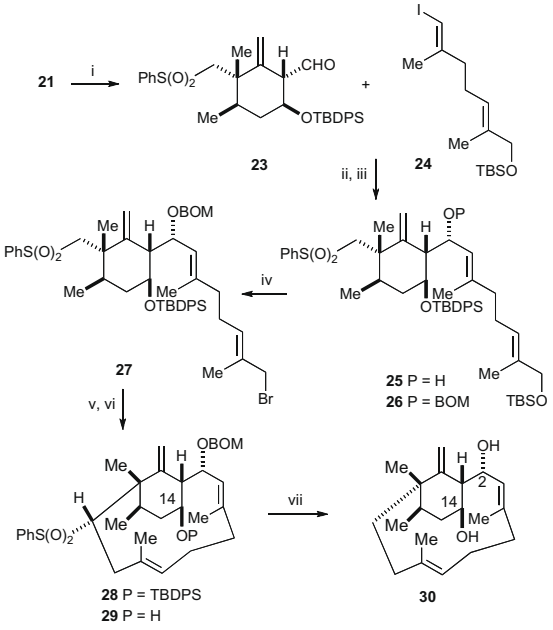
phenylthiomethyl substituents were trans-disposed with respect to the six-membered ring, as the major product. In contrast, rearrangement of the sulfone **18**, which required an excess of *n*-butyllithium, gave the homoallylic alcohol **21** in which the hydroxymethyl and phenylsulfonylmethyl substituents were cis-disposed with respect to the six-membered ring, see Scheme 2.[12]

The structure of the alcohol **21** prepared by rearrangement of the sulfone **18** was confirmed by X-ray crystallography later in the synthesis, vide infra, and was identical to the product prepared by oxidation of the minor product from rearrangement of sulfide **17**. Although the origin of this stereochemical dichotomy was not investigated, the need for 2 equiv of base for an efficient rearrangement of sulfone **18**, and the stereoselectivity of this rearrangement, are consistent with coordination of the lithiated sulfone with the ethereal oxygen directing the Wittig rearrangement to the face of the double bond cis to the lithiated sulfonyl methylene group, see the possible boat-like intermediate **22**.[12]

Addition of the vinyllithium reagent generated from the vinylic iodide **24**[13] to the aldehyde **23** prepared by oxidation of alcohol **21** using Parikh–Doering conditions,[15] was best achieved after transmetallation using ytterbium triflate[16] and gave alcohol **25** essentially as a single diastereoisomer, see Scheme 3. The stereose-



Scheme 2. Reagents and conditions: (i) ^{n}BuLi, THF, −50 °C (94%; **19**:**20** = 8:92); (ii) ^{n}BuLi (2 mol equiv), THF, −50 °C (**21**, 65%); (iii) ammonium molybdate, H_2O_2, EtOH, 0 °C (86%).



Scheme 3. Reagents and conditions: (i) py.SO_3, DMSO, DCM, ^{i}Pr$_2$NEt, rt (95%); (ii) **24**, ^{t}BuLi, −78 °C, 1 h, Yb(OTf)$_3$, −78 °C, 4.5 h (85%); (iii) BOMCl, ^{i}Pr$_2$NEt, TBAI, rt, 16 h (92%); (iv) (a) AcOH:H_2O:THF (3:1:1), rt, 2 days (80%) (b) MsCl, Et_3N, THF, 0 °C, 45 min, LiBr, THF, 1.5 h (92%); (v) **27** (0.05 M), NaHMDS (syringe pump, 40 min), THF, 0 °C, 30 min (85%); (vi) TBAF, THF, rt (95%); (vii) Na, NH_3, THF, EtOH, −78 °C, 2 days (95%).

lectivity of this reaction, which is consistent with chelation control, was also confirmed later in the synthesis by X-ray crystallography. Following protection of the alcohol as its benzyloxymethyl ether **26**, selective removal of the *tert*-butyldimethylsilyl group, mesylation and in situ treatment of the mesylate with lithium bromide, gave the bromide **27**. Cyclisation was achieved using sodium hexamethyldisilazide as base and gave the bicyclic sulfone **28** in an excellent yield (85%) as a single diastereoisomer. The structure of sulfone **28** was established by X-ray crystallography, see Figure 1, which also confirmed the earlier stereochemical assignments. Desilylation then gave alcohol **29**, and reductive desulfonylation under Birch conditions with cleavage of the benzyloxymethyl ether, gave diol **30**.

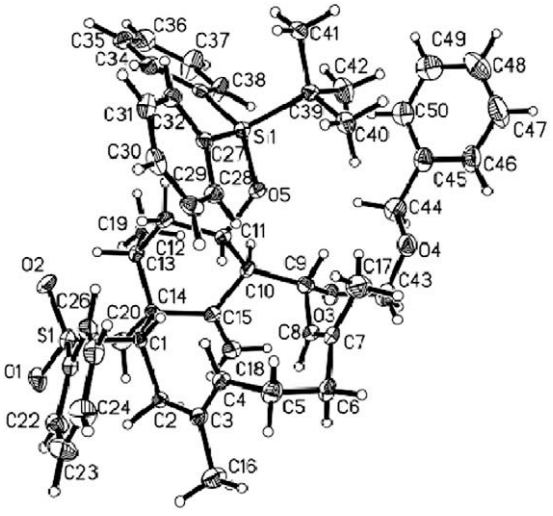
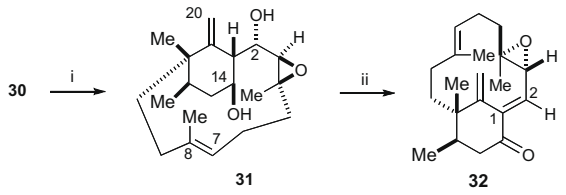


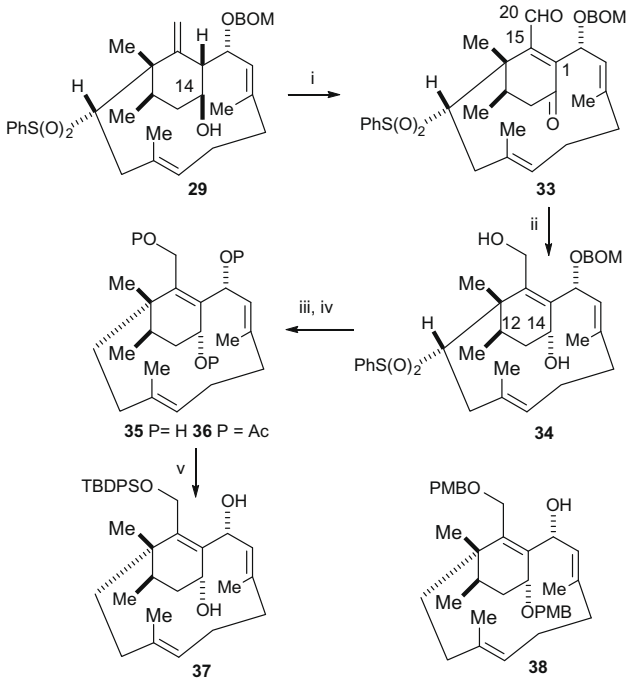
Figure 1. An ORTEP projection of the structure of sulfone **28** as determined by X-ray crystallography.[17]

Diol **30** has the carbon skeleton of phomactins with the required configuration at C(2) for directed epoxidation of the C(3)–C(4) double bond,[2a,b] albeit with the undesired configuration at C(14) for direct incorporation into phomactin A. Reaction with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ gave the required mono-epoxide **31**. However, attempts to introduce the oxygen functionality at C(20) by epoxidation of the exocyclic methylene group of mono-epoxide **31** were unsuccessful, secondary epoxidation instead taking place at the C(7)–C(8) double bond under microwave conditions. Interestingly, attempted oxidation of dihydroxyepoxide **31** to the corresponding diketone under the Parikh–Doering conditions[15] gave the α,β-unsaturated ketone **32**, the C(1)–C(2) double bond geometry provisionally being assigned by analogy with earlier work (Scheme 4).[18]

It was decided to study inversion of the configuration of the alcohol **29** at C(14) and formation of the tetrahydropyranyl ring present in phomactin A **1** before attempting oxidation of the exocyclic methylene group. Preliminary studies of oxidation of this alcohol using a range of oxidants including Parikh–Doering[15] or Swern conditions, the Dess–Martin periodinane, PDC or PCC, gave either returned starting material or complex mixtures of products. Initial studies of direct inversion using a Mitsunobu reaction were also unsuccessful. However, oxidation with tetrapropyl-ammonium perruthenate (TPAP)[19] gave a good yield of the unsaturated keto-aldehyde **33**, see Scheme 5.



Scheme 4. Reagents and conditions: (i) $VO(acac)_2$, TBHP, C_6H_6, rt, 30 min (85%); (ii) $py.SO_3$, DMSO, $^iPr_2NEt$, DCM, 0 °C, 5 min (50%).



Scheme 5. Reagents and conditions: (i) TPAP, NMO, 4 Å MS, DCM, rt, 1 h (78%); (ii) DIBAL-H, DCM, −78 °C, 1 h (80%); (iii) Na, NH_3, THF, EtOH, −78 °C, 1 h (95%); (iv) Ac_2O, Et_3N, DMAP, rt, 16 h (90%); (v) TBDPSCl, imid., DCM, rt, 16 h (55%).

The clean formation of keto-aldehyde **33** was unexpected. Analogous oxidations of homoallylic steroidal alcohols are known, but only modest yields are generally obtained unless ultrasound is used.[20] However, this oxidation of alcohol **29** has achieved several transformations required for its conversion into phomactin A including oxidation at C(14) and C(20), and the introduction of the C(1)–C(15)-double bond.

Reduction of keto-aldehyde **33** using di-isobutylaluminium hydride gave the diol **34**, the configuration assigned at C(14) being consistent with NOE studies including the enhancement of H(14) on irradiation of the 12-methyl group. Reductive removal of the sulfonyl and benzyloxymethyl groups under Birch conditions then gave the triol **35** and esterification gave the crystalline triacetate **36** the structure of which was confirmed by X-ray diffraction, see Figure 2.

The triol **35** would appear to be a useful advanced intermediate for a synthesis of phomactin A **1**. However, preliminary studies of epoxidation of its mono-*tert*-butyldiphenylsilyl ether **37** led to the formation of a significant amount of a bis-epoxide due to epoxidation of both the C(3)–C(4) and C(1)–C(15) double bonds, as well as the required C(3)–C(4)-mono-epoxide. This was to be expected since analogous results were observed by Pattenden during studies of the epoxidation of the corresponding bis-(4-methoxybenzyl) ether **38**,[2a,b] and so rather than attempt to optimise the mono-epoxidation of triene **37**, it was decided to introduce the C(3)–C(4)-epoxide before the TPAP oxidation, that is, before the introduction of the C(1)–C(15) double bond.

Oxidation of the unprotected dihydroxyepoxide **31** using TPAP gave a single product which was provisionally identified as the lactone **39**, see Scheme 6. However, preliminary attempts to reduce this using di-isobutylaluminium hydride gave complex mixtures of products and so, in order to avoid lactone formation, it was necessary to study the TPAP oxidation of an epoxide analogous to **31**, but with the 2-hydroxyl group protected.

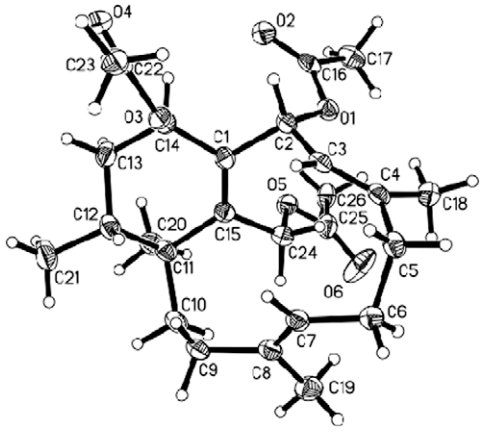
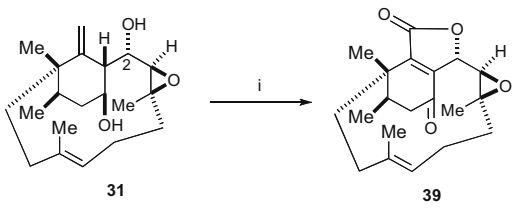


Figure 2. An ORTEP projection of the structure of the triacetate **36** as determined by X-ray crystallography.[17]

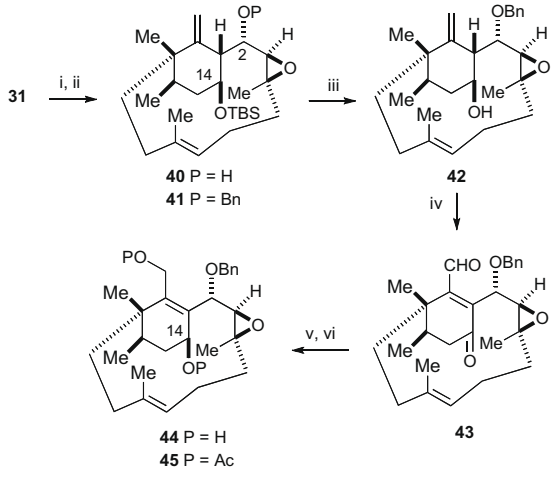


Scheme 6. Reagents and conditions: (i) TPAP, NMO, 4 Å MS, DCM, rt, 10 min (48%).

Regioselective monosilylation of the dihydroxyepoxide **31** gave the silyl ether **40**, see Scheme 7, and alkylation of the free hydroxyl group gave the benzyl ether **41** which was desilylated to give the required hydroxyepoxide **42**. Oxidation with TPAP proceeded as expected to give keto-aldehyde **43** but reduction using di-isobutylaluminium hydride gave mainly diol **44** which was shown to have the wrong configuration at C(14) by determination of the X-ray crystal structure of its diacetate **45**, see Figure 3.

The reductions of keto-aldehydes **33** and **43** using di-isobutylaluminium hydride proceed with opposite stereoselectivities with respect to the ketone functionality at C(14). This unexpected result may be due to the phenylsulfonyl group in keto-aldehyde **33** shielding the lower face of the 14-carbonyl group so directing hydride attack leading to the required configuration at C(14) in alcohol **34**. Keto-aldehyde **43** lacks the 10-phenylsulfonyl substituent and steric hindrance by the cis-disposed 12- and 13-methyl substituents would appear to dominate leading to the undesired configuration at C(14).

In our system, the phenylsulfonyl group at C(10) may be influencing the stereoselectivity of reduction of a ketone at C(14).



Scheme 7. Reagents and conditions: (i) TBSCl, imid., rt, 16 h (99%); (ii) KHMDS, BnBr, THF, −78 °C to rt, 16 h (99%); (iii) TBAF, THF, rt 16 h (99%); (iv) TPAP, NMO, 4 Å MS, DCM, rt, 1 h (62%); (v) DIBAL-H, DCM, −78 °C, 1 h [69% plus 11% of its epimer at C(14)]; (vi) Ac_2O, Et_3N, DMAP, rt, 16 h (99%).

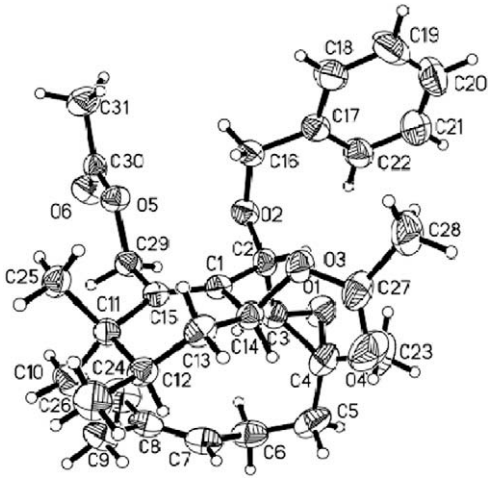


Figure 3. An ORTEP projection of the structure of the diacetate **45** as determined by X-ray crystallography.[17]

Moreover, the introduction of the C(3)–C(4) epoxide, which relies on the presence of a hydroxyl group at C(2), needs to take place before the introduction of C(1)–C(15) double bond. Therefore it would appear necessary to have a protecting group on the 2-hydroxyl substituent which can be removed without concomitant reductive cleavage of the phenylsulfone. Introduction of the C(3)–C(4)-epoxide, TPAP oxidation and DIBAL-H reduction, followed by reductive removal of the phenylsulfone, may then lead to phomactin A.

Conclusions

This work has led to advanced intermediates and provided useful chemical insight which may be useful in syntheses of phomactins. Of interest is the complementary stereoselectivity observed for [2,3]-Wittig rearrangements of the lithiated methyl ethers generated from the sulfide **17** and sulfone **18**, the oxidations using TPAP of the homoallylic alcohols **29**, **31** and **42**, and the stereochemical dichotomy observed during the reduction of the keto-aldehydes **33** and **43** using di-isobutylaluminium hydride. Present work is concerned with the further development of these studies and the completion of a synthesis of phomactin A **1**.

Acknowledgement

We thank the EPSRC for studentships (to M.J.K. and T.J.B.).

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12. Analogous [2,3]-Wittig rearrangements were investigated for (trimethylsilylethoxy)methyl (SEM) ethers corresponding to the *tert*-butyldiphenyl ethers **17** and **18** and for the epimeric SEM-ethers with the opposite configurations at C(3). In all cases the sulfones and sulfides rearranged with complementary stereoselectivity as observed for sulfide and sulfone **17** and **18**.
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17. *Crystallographic data for sulfone* **28**. $C_{50}H_{62}O_5SSi$, MW 803.15, monoclinic, space group $P2_1/c$, $a = 22.478(2)$, $b = 10.2390(11)$, $c = 21.361(2)$ Å, $\beta = 115.739(2)°$, $V = 4428.5(8)$ Å^3, $Z = 4$, Dc = 1.205 g cm^{-3}, μ(MoKα) = 0.146 mm^{-1}, $F(000) = 1728$, $T = 100$ K. Crystal dimensions were $0.4 \times 0.07 \times 0.02$ mm, 31,135 reflections measured, 7817 independent reflections ($R_{int} = 0.116$), $R_1 = 0.039$ for the 3559 reflections with $I > 2\sigma(I)$, w$R(F^2) = 0.112$ (all data). CCDC 712103. *Crystallographic data for triacetate* **36**. $C_{26}H_{38}O_6$, MW 446.56, orthorhombic, space group *Pbca*, $a = 16.269(3)$, $b = 10.618(2)$, $c = 28.038(6)$ Å, $V = 4843.2(18)$ Å^3, $Z = 8$, Dc = 1.225 g cm^{-3}, μ(MoKα) = 0.086 mm^{-1}, $F(000) = 1936$, $T = 100$ K. Crystal dimensions were $0.3 \times 0.3 \times 0.1$ mm, 21,743 reflections measured, 4275 independent reflections ($R_{int} = 0.071$), $R_1 = 0.044$ for the 2734 reflections with $I > 2\sigma(I)$, w$R(F^2) = 0.115$ (all data). CCDC 712105. *Crystallographic data for diacetate* **45.** $C_{31}H_{42}O_6$, MW 510.65, monoclinic, space group C2/c, $a = 40.309(3)$, $b = 8.6560(7)$, $c = 16.5661(13)$ Å, $\beta = 91.250(2)°$, $V = 5778.8(8)$ Å^3, $Z = 8$, Dc = 1.174 g cm^{-3}, μ(MoKα) = 0.080 mm^{-1}, $F(000) = 2208$, $T = 230$ K. Crystal dimensions were $0.6 \times 0.4 \times 0.3$ mm, 19,854 reflections measured, 5107 independent reflections ($R_{int} = 0.047$), $R_1 = 0.039$ for the 4036 reflections with $I > 2\sigma(I)$, w$R(F^2) = 0.114$ (all data). CCDC 712104. X-ray data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK: fax: +44 122 333 6033.
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