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Stereoselective synthesis and cyclisation of the acyclic precursor to auripyrone A and B

Michael V. Perkins,* Rebecca A. Sampson, John Joannou and Max R. Taylor

School of Chemistry, Physics and Earth Sciences, Flinders University, GPO Box 2100, 5001 South Australia, Australia

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Abstract—The acyclic precursor to the auripyrones has been synthesized by a stereoselective aldol strategy. This compound fails to undergo cyclisation to form the spiroacetal dihydropyrone ring system found in auripyrone A and B; instead, it forms a dihydropyrone ring by cyclisation of the C11 hydroxyl onto the C15 carbonyl with subsequent dehydration. In contrast, a model compound was prepared and shown to cyclise to both the spiroacetal dihydropyrone ring system and the dihydropyrone ring.

Auripyrones A (**1**) and B (**2**) are two polypropionate natural products isolated from Japanese specimens of the sea hare, *Dolabella auricularia* (Aplysiidae), in 1996 by Suenaga and co-workers[1] (Fig. 1). The structure was assigned, as shown, from extensive ^{1}H and ^{13}C spectroscopic analysis. [The C2′ configuration for auripyrone B (**2**) was not assigned.]

Notably the auripyrone ring system consisted of a highly substituted spiroacetal dihydropyrone in which all the alkyl substituents were positioned equatorially, except for the C-10[2] methyl which was axial. Both the acetal oxygens were determined to be axially oriented with respect to the other ring and hence were in the anomerically favoured positions. Auripyrones A and B were found to exhibit potent cytotoxic activity against HeLa S_3 cells with IC_{50} values of 0.26 μg/mL and 0.48 μg/mL, respectively.[1]

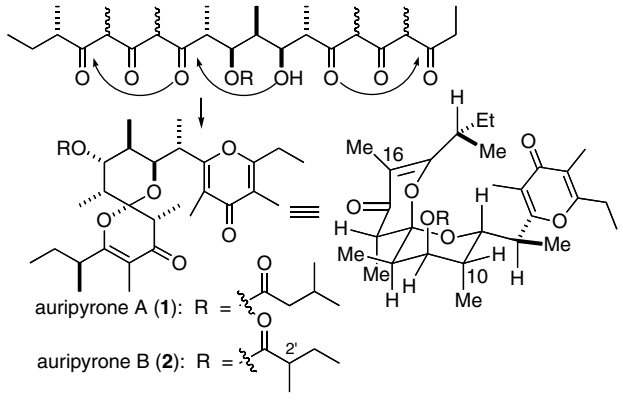

Figure 1.

The putative acyclic precursor to the auripyrones contains a degree of symmetry with a central stereopentad, a remote stereocentre (C18) and two triones. With the *pseudo* symmetry of the system broken by the acyl group, the free hydroxyl initiates a spiroacetalisation dehydration with one trione while the other trione cyclises to form the γ-pyrone ring.

We have previously reported the synthesis of a C10 epimeric model spiroacetal dihydropyrone,[3] and we now report the synthesis of the correct C10 model spiroacetal dihydropyrone and the attempted cyclisation of the acyclic precursor to the auripyrones. Scheme 1 shows the proposed retrosynthesis of the auripyrones. It was anticipated that deprotection of acyclic precursor **3** would allow the cyclisation dehydration cascade to form the spiroacetal dihydropyrone and that subsequent acylation would give auripyrones A (**1**) or B (**2**). Triketone **3** was proposed to be formed from an aldol coupling between ketone **4** and aldehyde **5**, followed by oxidation. Oxidation and cyclisation of compound **6** would form the pyrone ring and subsequent removal of the Evans auxiliary was proposed to give aldehyde **5**. Aldol reaction between aldehyde **7** and ketone **8** was anticipated to give compound **6**. Compound **7** was to be prepared by a substrate directed hydroboration followed by

* Corresponding author. Tel.: +61 8 8201 2496; fax: +61 8 8201 2905; e-mail: mike.perkins@flinders.edu.au

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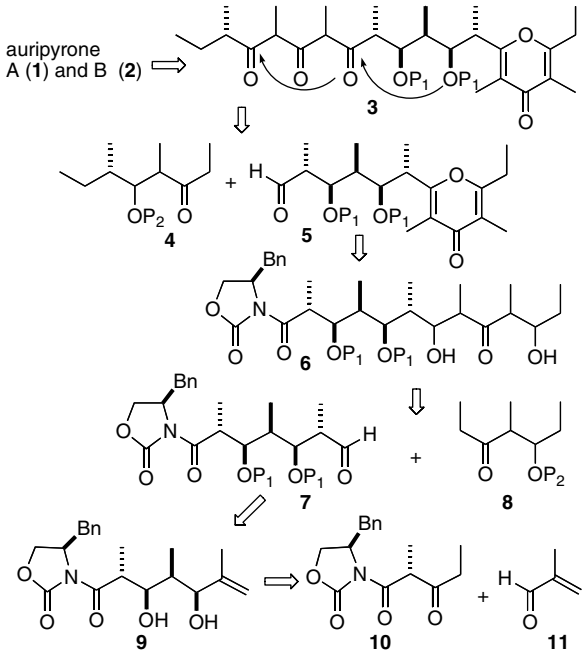


Scheme 1. Retrosynthesis of auripyrones A (**1**) and B (**2**).

oxidation of compound **9**. A stereoselective aldol, in a reduction sequence using the Evans dipropionate **10**[4] and methacrolein (**11**), generates the required stereotetrad present in **9**.

Prior to the synthesis of the complex acyclic precursor to the auripyrones, a model compound was prepared and cyclised. The model compound **12** (Fig. 2) contains the correct C9–C17 spiroacetal ring system but lacks the γ-pyrone ring and the stereocentre at C18. Instead, the spiroacetal dihydropyrone is flanked by two isopropyl groups at C9 and C17. Generation of the required stereotetrad was anticipated to be straightforward, based on the previous results.[5]

The stereoselective synthesis of racemic compound **13** is shown in Scheme 2. The Ti(IV)-mediated aldol reaction[6] of 2-methylpentan-3-one (**14**) with methacrolein (**11**) (90% ds), followed by *syn* reduction[7] (>97% ds) with DIBAL-H, gave diol **15**. The *syn* stereochemistry of reduction was confirmed by protection of the diol **15** as acetonide **16** and by subsequent analysis of the ^{1}H and ^{13}C NMR.[8] Protection of the diol as the di-*tert* butylsilylene[9] (91%), followed by stereoselective hydroboration

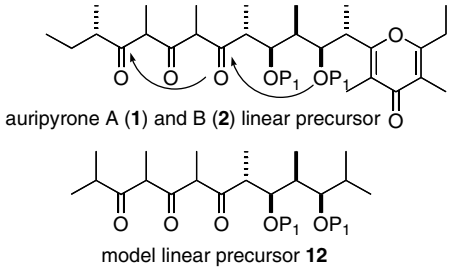
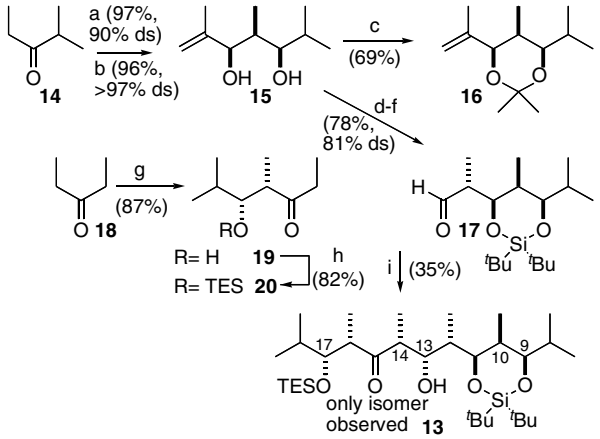


Figure 2.

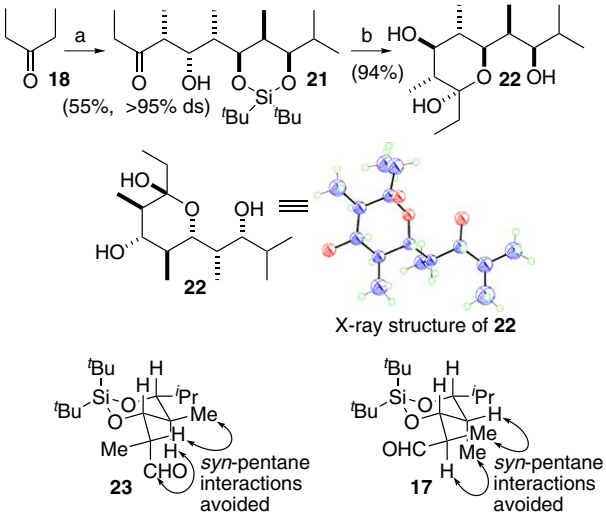


Scheme 2. Reagents and Conditions: (a) (i) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.1 equiv); (iii) methacrolein (**11**) (2 equiv), −78 °C, 2 h; (b) DIBAL-H (3 equiv), −78 °C, 4 h, →−25 °C; (c) $(CH_3)_2C(OCH_3)_2$, PPTS, rt, 3 h; (d) $^{t}Bu_2Si(OTf)_2$ (2 equiv), 2,6-lutidine (3.5 equiv), CH_2Cl_2, 40 °C, 24 h; (e) (i) $[ThexBH_2]_2$·TMEDA (3 equiv), THF, rt, 48 h; (ii) H_2O_2, 10% NaOH, THF, rt, 20 h; (f) PCC (4 equiv), CH_2Cl_2, (g) (i) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.1 equiv), 1.5 h; (iii) isobutyraldehyde (2 equiv), 1.5 h, −78 °C → −50 °C; (h) pyridine (2 equiv), TES-triflate (1 equiv), −78 °C, 30 min, −78 °C→rt, 2 h; (i) (i) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.1 equiv), 1 h; (iii) aldehyde **17** (0.5 equiv), 1.5 h, −78 °C→−50 °C, 30 min; (iv) pH 7 buffer.

with $[ThexBH_2]_2$·TMEDA[10] (88%, 81% ds) and oxidation with PCC gave aldehyde **17** (98%).

The Ti(IV)-mediated aldol reaction[6] of pentan-3-one (**18**) with isobutyraldehyde gave ketone **19** with a high level of *syn* selectivity (90% ds, the major isomer could be separated) (Scheme 2). Protection of the triethylsilyl ether gave ketone **20**, ready for aldol coupling with aldehyde **17**. Precomplexation of **20** with $TiCl_4$ at −78 °C for 30 min, followed by the addition of diisopropylethylamine and aldehyde **17** remarkably gave a racemic mixture of a single diastereomer assigned as compound **13** in rather poor yield (35%). Formation of the single racemic product **13** from the coupling of two racemic fragments is an unusual example of mutual kinetic diastereoselection. In this case, a large Felkin preference[11] of aldehyde **17** is matched in a *fast* reaction with the *syn–syn* preference of ketone **20**. Thus, each enantiomer of the enolate of ketone **20** selectively reacts with the correct enantiomer of aldehyde **17**.

Direct proof of the stereochemistry of compound **13** was not possible, but the Felkin preference of aldehyde **17** was determined by reaction with the Ti(IV) enolate of pentan-3-one (**18**) (Scheme 3). In this case, reaction with the achiral enolate again gave a single detectable product **21** in 55% yield. Deprotection of product **21** using HF–pyridine buffered with excess pyridine (HF·pyr/pyr) gave hemiacetal **22**, which formed crystals suitable for single crystal X-ray analysis.[12] This proved the structure of hemiacetal **22** and thus the structure of compound **21** as shown. The high Felkin preference for aldehyde **17** is in stark contrast to the previously reported[3] *anti*-Felkin preference of the γ-epimeric aldehyde **23**. The underlying cause of this switch in facial

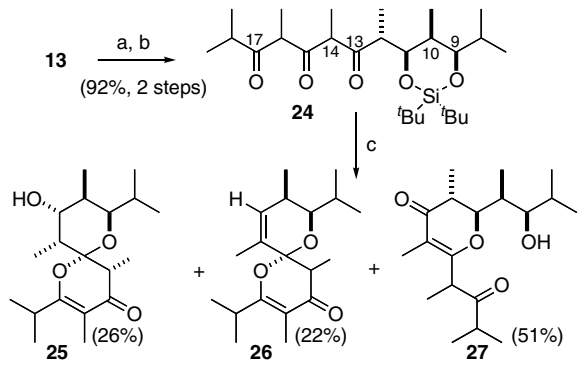


Scheme 3. Synthesis and X-ray structure (displacement ellipsoids at 50% level) of hemiacetal **22**. Reagents and Conditions: (a) (i) $TiCl_4$ (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^iPr_2EtN$ (1.2 equiv), 1 h; (iii) aldehyde **17** (0.5 equiv), 45 min, −78 °C→−30 °C; (b) HF·pyr/pyr, rt, 2 h.

selectivity of the aldehyde is the change in conformation of the C11–C12 bond in the rigidly held cyclic silylene, such that *syn* pentane interactions are avoided with the C10 methyl (Scheme 3).[13]

Removal of the TES protecting group from **13** was achieved with *p*-TSOH, and Dess–Martin oxidation gave triketone **24** (enol forms were present from spectroscopic analysis). Deprotection with HF·pyr/pyr gave a complex mixture of diols and hemiacetals but treatment with *p*-TsOH resulted in the formation of three cyclised products, as shown in Scheme 4.

The first compound (26%) which was identified by ^1H and ^{13}C NMR analysis as the desired cyclised product was spiroacetal dihydropyrone **25**.[14] The second product (22%) showed similar ^1H and ^{13}C NMR spectra except for an apparent dehydration of the C11 hydroxyl, giving a C11–C12 double bond and was thus



Scheme 4. Synthesis of spiroacetal dihydropyrone **25**. Reagents and conditions: (a) *p*-TSOH, CH_2Cl_2/MeOH; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (c) (i) HF·pyr/pyr, rt, 2 h; (ii) *p*-TsOH, rt, 3 h.

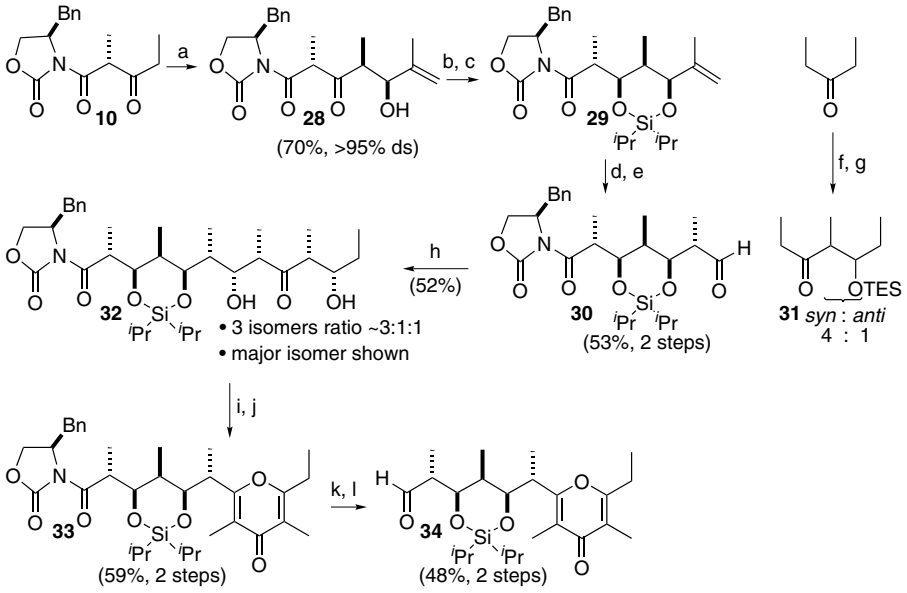
assigned as compound **26**. (The configuration at the C14 methyl could not be assigned.) These first two products were analogous to those obtained previously.[3] A third product (55%), assigned as dihydropyrone **27**, was formed by the alternative cyclisation of the C11 hydroxyl onto the C15 carbonyl and subsequent dehydration. In contrast to our previous model system, the presence of the *axial* methyl in this sprioacetal system partly tips the balance towards this alternative undesired cyclisation.

Despite the modest yield obtained in the model cyclisation, the enantiomerically pure linear precursor to auripyrone was prepared (Schemes 5 and 6). Reaction of the Sn(II) enolate[6a] of the Evans dipropionate equivalent[4] ketone **10** with methacrolein (**11**) proceeded with high selectivity giving the *syn–anti* product **28** in good yield as the only detectable isomer. Reduction with DIBAL-H again gave good *syn* selectivity.[7]

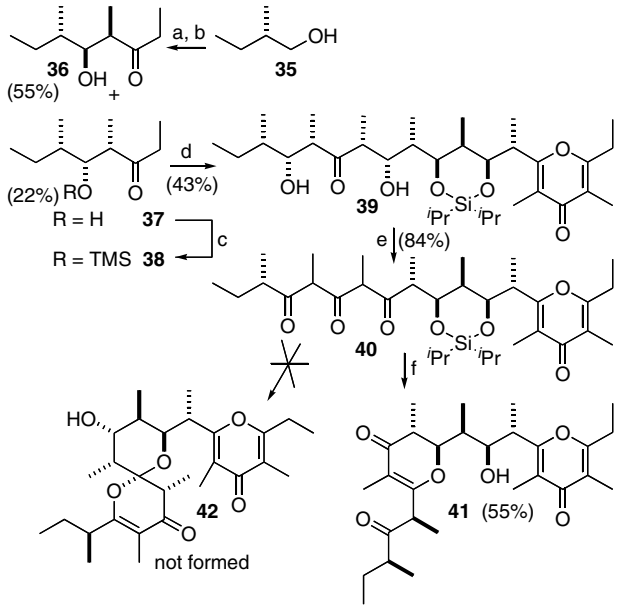
The poor yields in the aldol reactions of aldehyde **17** were attributed to the steric bulk of the protecting group, and in an attempt to reduce this the ^{t}Bu groups were replaced with ^{i}Pr groups on the silyene. Thus, protection of the diol was carried out using $^iPr_2Si(OTf)_2$and 2,6-lutidine, giving compound **29**. Hydroboration ([Thex-BH_2]$_2$·TMEDA[10]) and oxidation (PCC) gave aldehyde **30**. Aldol reaction of aldehyde **30** with the Ti(IV) enolate[6] of ketone **31** (as a racemic 4:1 *syn:anti* mixture) gave a mixture of isomers of **32**. (The TES group was removed under the reaction or product isolation conditions.) The major isomer was assigned as the product of aldehyde **30** coupling with the matched enantiomer[6c,d] of the major *syn* isomer of ketone **31**. Oxidation to the trione (Dess–Martin Periodinane[15]), followed by treatment with Ph_3P/CCl_4[16] gave pyrone **33**. Reductive removal of the Evans auxiliary with $LiBH_4$, followed by oxidation (Dess–Martin Periodinane[15]) gave aldehyde **34**.

Reaction of 2-(*S*)-2-methylbutanal (prepared by oxidation of the commercially available alcohol **35**) with the Ti(IV) enolate[6] of pentan-3-one (**18**) gave the separable enantiomerically pure ketones **36** (55%) and **37** (22%) (Scheme 6). The minor (Felkin[11b]) product **37** was used as it was assumed to be matched[6c,d] with the facial preference of aldehyde **34**. Protection of **37** as the TMS ether **38**, followed by formation of the Ti(IV) enolate and reaction with aldehyde **34**, gave as expected a single isomer of product **39**. Oxidation of **39** (Dess–Martin Periodinane[15]) gave trione **40**. Unfortunately, deprotection (HF·pyr/pyr) and treatment with *p*-TsOH resulted only in the formation of the unwanted cyclised product **41**, with none of the desired spiroacetal dihydropyrones **42**.

In conclusion, we have shown the successful cyclisation–dehydration of a suitable trione precursor to give a model spiroacetal dihydropyrone **25**, analogous to that found in the marine natural products auripyrone A (**1**) and B (**2**). But extension of this approach to the synthesis of auripyrones failed to yield the desired cyclisation. Successful cyclisation to form the spiroacetal



Scheme 5. Synthesis of pyrone **34**. Reagents and conditions: (a) (i) tin(II) triflate 1.3 equiv, CH_2Cl_2, −20 °C, Et_3N, 10 min, amide **10**, 1 h, −78 °C→−50 °C; (ii) methacrolein (**11**), 1.5 equiv, 30 min, −78 °C→−15 °C; (b) DIBAL-H, 4 equiv, −78 °C; (c) $^{i}Pr_2Si(OTf)_2$ (2 equiv), 2,6-lutidine (3.5 equiv), CH_2Cl_2, 25 °C, 18 h; (d) (i) $[ThexBH_2]_2$·TMEDA (2 equiv), THF, rt, 72 h, 40 °C, 24 h; (ii) H_2O_2, MeOH, THF, rt, 2 h; (e) PCC (4 equiv), CH_2Cl_2; (f) (i) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.5 equiv), 1.5 h; (iii) propanal (2 equiv), 1.5 h, −78 °C → 0 °C; (g) pyridine (2 equiv), TES-triflate (1 equiv), 0 °C, 15 h; (h) (i) ketone **31**, $TiCl_4$ (2.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (2.5 equiv), 1 h; (iii) −78 °C → −85 °C, aldehyde **30** (0.5 equiv), −85 °C → −5 °C; (iv) pH 7 buff. (i) Dess–Martin periodinane, CH_2Cl_2, rt, 4 h; (j) Ph_3P (12 equiv), CCl_4 (12 equiv), THF, 3 d; (k) $LiBH_4$ (20 equiv), Et_2O, −10 °C (l) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h.



Scheme 6. Attempted synthesis of spiroacetal dihydropyrone **42**. Reagents and conditions: (a) (i) $COCl_2$, DMSO, −78 °C, alcohol **35**, Et_3N, 15 min, −78 °C→−5 °C; (b) (i) pentan-3-one (**18**), $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.5 equiv), 1.5 h; (iii) aldehyde (0.8 equiv), 1 h, −78 °C→−5 °C; (c) pyridine (2 equiv), TMS-Cl (1.2 equiv), −78 °C→0 °C, 1 h; (d) (i) $TiCl_4$ (1.2 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.3 equiv), 1 h; (iii) −78 °C→−90 °C, aldehyde **34** (0.2 equiv), 2 h, −78 °C→−10 °C; (iv) pH 7 buffer; (e) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (f) (i) HFpyr/pyr, rt, 2 h; (ii) *p*-TsOH, rt, 1 h.

dihydropyrone in the auripyrones appears to require differential protection of the C9 and C11 hydroxyls.

Acknowledgements

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Supplementary data

A short discussion of the facial selectivities of aldehydes **23** and **17** in aldol reactions is available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.096.

References and notes

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11. (a) This facial selectivity is opposite to the more usually observed *anti*-Felkin facial preference of α-chiral aldehydes in aldol reactions of *Z* enolates; For a discussion of the facial preference of α-chiral aldehydes see: (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
12. Crystal data for compound **22**: $C_{15}H_{30}O_4$, $M_W = 273.39$, space group $I4_1cd$ with $a = 28.109(9)$ Å, $b = 28.109(9)$ Å, $c = 9.096(5)$ Å, $V = 7187(6)$ Å^3, $T = 168(2)$ K, $Z = 16$, density (calc) $= 1.014$ g cm^{-3}, $F(000) = 2432$, μ(MoKα) $= 0.072$ mm^{-1}. A total of 44,205 intensity data were measured on a Bruker P4 CCD area detector diffractometer using a $0.10 \times 0.11 \times 0.60$ mm^3 crystal giving 1911 unique reflections. One thousand five hundred and eighty eight reflections with $F^2 > 0$ (reflns/paras = 9.2) were used in the refinement; $R(F^2 > 2\sigma F^2) = 0.039$, $R_w = 0.068$. Crystallographic data (excluding structure factors) for the structure **22** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 293472. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
13. (a) See Supplementary data for a more detailed discussion; (b) Joannou, J. PhD Thesis, Flinders University, 2003.
14. All new compounds gave spectroscopic data in agreement with the assigned structures. Compound **25** had ^1H NMR ($CDCl_3$, 600 MHz): δ 3.58 (1H, dd, $J = 3.6$, 3.0 Hz, H-11), 3.42 (1H, dd, $J = 10.2$, 2.4 Hz, H-9), 2.97 (1H, sept, $J = 6.9$ Hz, H-18), 2.84 (1H, q, $J = 7.2$ Hz, H-14), 2.05 (1H, dq, $J = 7.2$, 3.3 Hz, H-12), 1.92 (1H, m, H-10), 1.66 (3H, s, H-24), 1.62 (1H, m, H-8), 1.55 (1H, br s, OH), 1.12 (3H, d, $J = 6.9$ Hz, H-19), 1.1 (3H, d, $J = 6.9$ Hz, H-25), 1.09 (3H, d, $J = 7.2$ Hz, H-22), 1.08 (3H, d, $J = 7.2$ Hz, H-23), 0.8 (3H, d, $J = 7.2$ Hz, H-21), 0.72 (3H, d, $J = 7.2$ Hz, H-7), 0.7 (3H, d, $J = 7.2$ Hz, H-20). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 194.6 (C-15), 166.8 (C-17), 108.4 (C-13), 108.3 (C-16), 75.7 (C-11), 73.1 (C-9), 44.6 (C-14), 36.5 (C-10), 32.1 (C-12), 30.1 (C-18), 28.9 (C-8), 20.5 (C-19), 19.9 (C-7), 19.4 (C-25), 17.9 (C-20), 12.5 (C-21), 10.3 (C-22), 8.2 (C-24), 7.6 (C-23). Compound **26** had ^1H NMR ($CDCl_3$, 600 MHz): δ 5.85 (1H, dd, $J = 5.4$, 1.8 Hz, H-11), 3.33 (1H, dd, $J = 10.2$, 2.7 Hz, H-9), 2.9 (1H, qn, $J = 6.9$ Hz, H-18), 2.85 (1H, q, $J = 6.9$ Hz, H-14), 2.10–2.04 (1H, m, H-10), 1.73 (3H, s, H-22), 1.72 (3H, s, H-24), 1.62–1.54 (1H, m, H-8), 1.119 (3H, d, $J = 6.9$ Hz, H-19), 1.116 (3H, d, $J = 6.9$ Hz, H-25), 1.02 (3H, d, $J = 6.9$ Hz, H-23), 0.85 (3H, d, $J = 7.2$ Hz, H-21), 0.82 (3H, d, $J = 7.2$ Hz, H-7), 0.8 (3H, d, $J = 7.2$ Hz, H-20). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 194.6 (C-15), 170.0 (C-17), 133.6 (C-11), 130.5 (C-12), 106.9 (C-16), 104.0 (C-13), 76.9 (C-9), 44.2 (C-14), 30.5 (C-10), 30.4 (C-18), 28.8 (C-8), 19.8 (C-25), 19.7 (C-7), 19.3 (C-19), 18.2 (C-22), 18.2 (C-20), 12.0 (C-21), 8.7 (C-24), 8.5 (C-23). Compound **27** had ^1H NMR ($CDCl_3$, 600 MHz): δ 3.91 (1H, dd, $J = 13.8$, 3 Hz, H-11), 3.81 (1H, q, $J = 6.6$ Hz, H-16), 3.34 (1H, dd, $J = 6.6$, 4.8 Hz, H-9), 2.63 (1H, sept, $J = 6.9$ Hz, H-18), 2.43 (1H, dq, $J = 13.8$, 7.2 Hz, H-12), 1.88–1.82 (1H, m, H-10), 1.77 (3H, s, H-23), 1.74–1.64 (2H, m, H-8 and OH), 1.19 (3H, d, $J = 6.6$ Hz, H-24), 1.03 (3H, d, $J = 6.9$ Hz, H-25), 1.01 (3H, d, $J = 6.9$ Hz, H-19), 1.0 (3H, d, $J = 7.2$ Hz, H-22), 0.9 (3H, d, $J = 6.9$ Hz, H-20), 0.89 (3H, d, $J = 6.9$ Hz, H-21), 0.85 (3H, d, $J = 6.9$ Hz, H-7). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 211.0 (C-17), 194.9 (C-13), 168.1 (C-15), 110.2 (C-14), 87.3 (C-11), 79.4 (C-9), 47.0 (C-16), 40.9 (C-12), 39.9 (C-18), 36.0 (C-10), 30.6 (C-8), 19.7 (C-7), 19.1 (C-25), 18.0 (C-19), 17.5 (C-20), 13.5 (C-24), 9.5 (C-23), 9.4 (C-22), 7.0 (C-21). Compound **39** had ^1H NMR ($CDCl_3$, 300 MHz): 4.18 (1H, dd, $J = 7.2$, 2.7 Hz, C*H*O), 4.16 (1H, dd, $J = 8.1$, 1.8 Hz, C*H*O), 3.99 (1H, dd, $J = 8.7$, 1.8 Hz, C*H*O), 3.59 (1H, dd, $J = 7.5$, 3.3 Hz, C*H*O), 3.20–3.10 (1H, m, C*H*C=O), 3.02 (1H, dq, $J = 7.2$, 6.9 Hz, vinyl C*H*CH$_3$), 2.91 (1H, dq, $J = 7.2$, 3.6 Hz, C*H*C=O), 2.61 (2H, q, $J = 7.5$ Hz, vinyl CH_2CH$_3$), 1.96 (3H, s, vinyl CH_3), 1.95 (3H, s, vinyl CH_3), 1.86–1.80 (1H, m, C*H*CH$_3$), 1.76–1.65 (1H, m, C*H*CH$_3$), 1.50–1.37 (2H, br s, 2 × OH), 1.24 (3H, d, $J = 6.9$ Hz, CHCH_3), 1.21 (3H, t, $J = 7.5$ Hz, CH$_2$CH_3), 1.14 (3H, d, $J = 7.2$ Hz, CHCH_3), 1.08 (3H, d, $J = 6.9$ Hz, CHCH_3), 1.01–0.86 (29H, m, 8 × CHCH_3, 2 × SiC*H*CH$_3$, CH_2CHCH$_3$, CH$_2$C*H*CH$_3$). ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 219.7, 179.9, 164.5, 163.8, 119.7, 117.7, 79.9, 79.4, 74.3, 71.9, 49.7, 47.1, 40.0, 39.3, 36.8, 34.5, 25.6, 24.7, 17.5, 17.3, 16.9, 16.88, 14.7, 13.5, 13.3, 12.6, 11.9, 11.4, 11.0, 10.6, 10.2, 9.7, 9.6, 3.8; ESMS Calculated for $C_{34}H_{60}O_7Si$ $[M+Na]^+$: 631.4001; found 631.4006; $[\alpha]_D^{20}$ −2.65 (*c* 0.753, $CHCl_3$).
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