Synthesis of a Ceramide Sphingolipid as a Potential Sex Pheromone of the Hair Crab *Erimacrus isenbeckii* Using Butane-2,3-diacetal Desymmetrised Glycolic Acid Building Blocks

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Abstract: A stereoselective synthesis of a ceramide sphingolipid as a potential sex pheromone of the hair crab *Erimacrus isenbeckii* is reported using diastereoselective alkylation and aldol reactions of butane-2,3-diacetal (BDA) desymmetrised glycolic acid building blocks as the key synthetic steps.

Key words: acetals, chiral auxiliaries, pheromones, sphingolipids, stereoselective synthesis

The ceramides shown in Figure 1 were isolated by Fusetani et al. from water containing post-moult female hair crabs of the species *Erimacrus isenbeckii*.[3] A sponge soaked in the ceramide mixture was shown to induce guard and copulatory behaviour in male hair crabs. Closely related compounds have been previously reported which are phospholipase A2 inhibitors[4] or exhibit cytotoxicity against tumour cells in mice.[5] The ceramide mixture was subsequently synthesised by Fusetani and coworkers from galactose pentaacetate and 9-bromononanol,[6] and the pheromone **1** was later synthesised by Masuda et al. from 12-bromododecanol and the Garner aldehyde.[7]

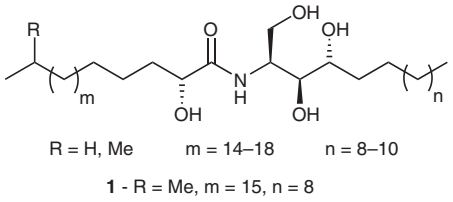


Figure 1 Ceramides isolated from water containing post-moult female hair crabs.

We planned to synthesise ceramide **1** using the butane-2,3-diacetal (BDA) desymmetrised glycolic acid building blocks developed in our group for the asymmetric synthesis of α-hydroxycarbonyl compounds.[8] The enantiomeric lactones **2** and **3** (Figure 2) are readily available in multigram quantities from 1-chloropropane-2,3-diol[8a,f] or from mannitol or ascorbic acid[8h] and undergo highly diastereoselective reactions with a wide range of electrophiles.

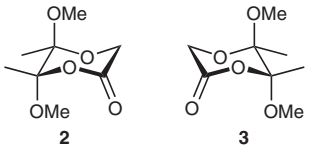
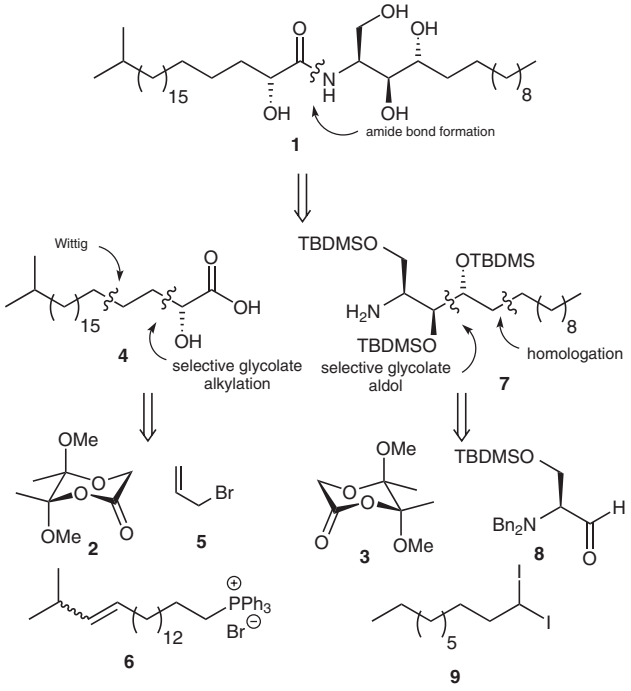


Figure 2 Enantiomeric butane-2,3-diacetal desymmetrised chiral glycolate equivalents.

We have previously demonstrated the use of lactones **2** and **3** in a total synthesis of the phytotoxic agent Herbarumin II.[9]

We intended to construct the hydroxyacid fragment **4**, using a stereoselective alkylation of glycolate **2** with allyl bromide **5**, followed by introduction of the long side chain via a Wittig olefination with phosphonium salt **6**, after oxidative cleavage of the alkene (Scheme 1). The *anti*-diol motif in amine **7** was to be constructed by an aldol reaction between glycolate **3** and the suitably protected serine-derived aldehyde **8**.[10]



Scheme 1 Retrosynthetic analysis of ceramide **1**.

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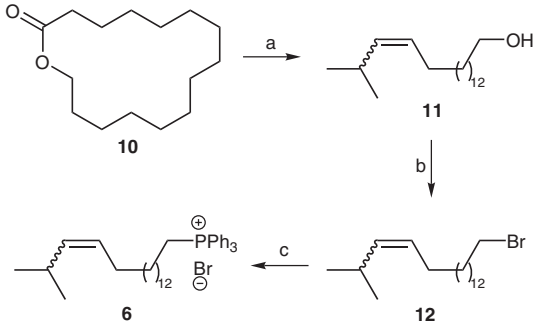
According to our experience, this should represent a matched aldol reaction between the two chiral units **3** and **8**, leading to a single diastereomeric product.[8b,g] The amine fragment **7** would then be obtained by conversion of the lactone functionality into an aldehyde and homologation with diiodide **9**.

The required long chain phosphonium salt **6** was synthesised from commercially available pentadecanolide **10** (Scheme 2). One-pot DIBALH reduction of **10** and Wittig olefination gave alcohol **11** in excellent yield. Bromination of the resulting alcohol **11** proceeded smoothly with triphenylphosphine dibromide[11] to give bromide **12** in 99% yield, and displacement with triphenylphosphine gave the phosphonium salt **6** in quantitative yield.

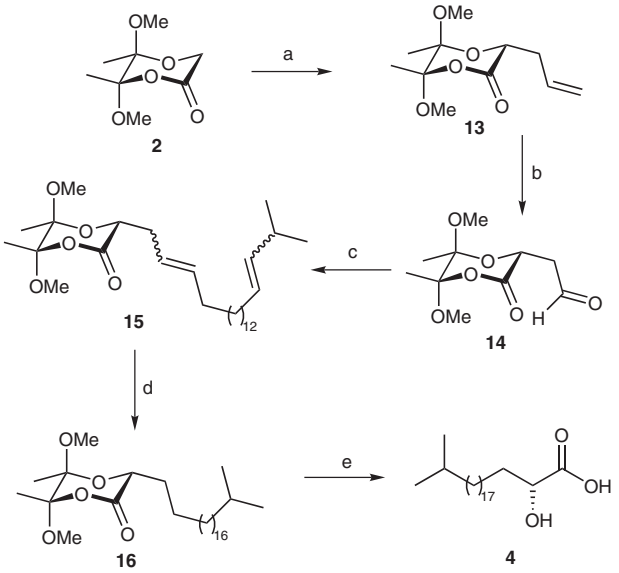


Scheme 2 a) DIBALH (1.5 equiv), PhMe, –78 °C, then MeOH (0.5 equiv), then *n*-BuLi (2 equiv), *i*-BuPPh$_3$Br (2 equiv), THF, –78 °C to r.t., 83%; b) PPh$_3$Br$_2$ (2.6 equiv), pyridine, MeCN, 99%; c) PPh$_3$ (1.0 equiv), neat, 120 °C, 100%.

With the salt **6** in hand, lactone **2** was alkylated stereoselectively with allyl bromide **5** to give the highly crystalline alkene **13** in very good yield (Scheme 3).[8a,f] Oxidative cleavage of alkene **13** to the aldehyde **14** proved problematic under a variety of conditions (O$_3$, OsO$_4$ and NaIO$_4$, etc.), almost certainly due to the unstable nature of **14**. Consequently, a one-pot oxidative cleavage and in situ Wittig olefination was carried out to yield dialkene **15** directly, albeit in a moderate 26% yield. Reduction of the double bonds with hydrogen and catalytic rhodium on alumina gave the lactone **16** in 87% yield, and straightforward acidic deprotection of the BDA group provided the desired α-hydroxyacid **4** in quantitative yield.

N,*N*-Dibenzyl protected aldehyde **8** (Scheme 4) was selected as a suitable coupling partner for the aldol reaction with lactone **3**. The aldehyde was readily obtained by LiBH$_4$ reduction in diethyl ether–methanol[12] of commercially available protected serine **17**, followed by Swern oxidation. Due to the sensitivity of aldehyde **8**,[10] it was prepared and used immediately without chromatographic purification.

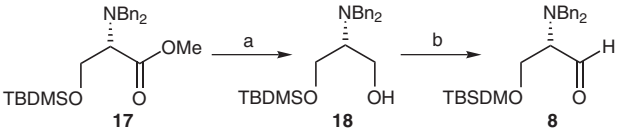
The aldol reaction proceeded smoothly with lactone **3** under standard conditions[8b,g] to yield the alcohol **19** as a single crystalline diastereoisomer (Scheme 5). The relative and absolute stereochemistry was readily confirmed at this point by single crystal X-ray diffraction.[13] The synthesis of alcohol **19** constitutes an extremely concise route to a protected form of the side chain of the phosphatase inhibitor calyculin A, with the correct relative (but opposite absolute) stereochemical features.[14]



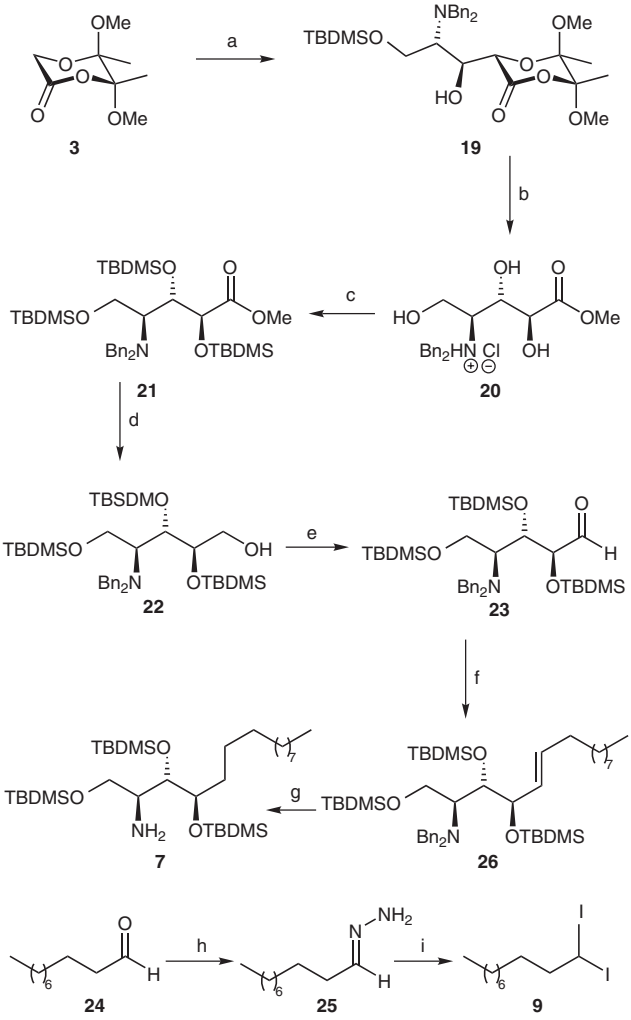
Scheme 3 a) LHMDS (0.95 equiv), THF, –78 °C, then CH$_2$=CHCH$_2$Br, –45 °C to r.t., 82%; b) O$_3$, CH$_2$Cl$_2$, –78 °C, then Me$_2$S (2 equiv); c) *n*-BuLi (1.8 equiv), **6** (0.9 equiv), THF, 26% from **6**; d) H$_2$, Rh/alumina, MeOH, 87%; e) TFA, H$_2$O, 100%.

Deprotection of the acid labile protecting groups, followed by global TBS protection of the alcohols gave the *tris*-TBS ether **21** in 93% yield over the two steps. The ester was reduced to the alcohol **22** with DIBALH in 62% yield, then oxidised to aldehyde **23** in good yield under Swern conditions.

Attempts at Wittig olefination of aldehyde **23** with *n*-decyltriphenylphosphonium bromide were unsuccessful under a variety of conditions, yielding only unreacted starting aldehyde. A report in the literature of a similarly unreactive aldehyde[15] indicated that a Takai olefination[16] might be successful. The required diiodide **9** was synthesised from decanal **24**, following the procedure of Sternhell and Pross (Scheme 5).[17] The subsequent olefination between diiodide **9** and aldehyde **23** finally yielded the desired alkene **26** in a moderate 33% yield. Hydrogenation of the alkene, with concomitant removal of the benzyl groups proceeded in good yield to give the known serinolipid **7**.[7]



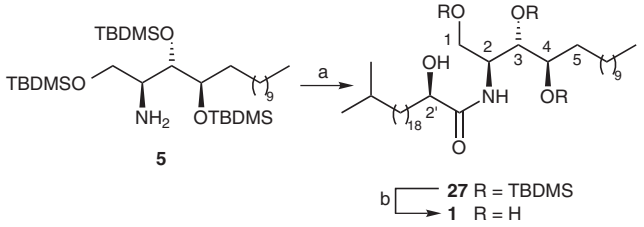
Scheme 4 a) LiBH$_4$ (3.9 equiv), MeOH, Et$_2$O, 0 °C to r.t., 95%; b) DMSO (4.5 equiv), (COCl)$_2$ (2.3 equiv), Et$_3$N (9 equiv), CH$_2$Cl$_2$, –78 °C, 97%.



Scheme 5 a) LHMDS (1.05 equiv), THF, –78 °C, then **8** (1.1 equiv), 90%; b) AcCl, MeOH; c) TBSOTf (5.2 equiv), 2,6-lutidine (7 equiv), CH_2Cl_2, 0 °C to r.t., 93% over two steps; d) DIBALH (2.9 equiv), CH_2Cl_2, 0 °C, 62%; e) DMSO (3.8 equiv), $(COCl)_2$ (1.9 equiv), Et_3N (16.8 equiv), –78 °C to r.t., 87%; f) **9** (3 equiv), $CrCl_2$ (12 equiv), DMF, THF, 33%; g) H_2, Pd/C, EtOH, 82%; h) hydrazine hydrate (7.9 equiv), 100 °C, 100%; i) Et_3N, I_2, CCl_4, 13%.

We were able to improve on the literature procedure for coupling amine **7** with the hydroxyacid fragment **4**, by using unprotected α-hydroxyacid **4** directly in the amide bond formation, rather than the corresponding *tert*-butyldimethylsilyl ether[7] or acetate.[6] Amide coupling with *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) proceeded in a gratifying 97% yield, and deprotection of the remaining silyl ethers gave the sex pheromone **1** in 78% yield (Scheme 6). The spectral data for **1** were in agreement with literature values.[6,7,18]

In conclusion, we have demonstrated that diastereoselective alkylation and aldol reactions of lactones **2** and **3** are readily scaleable and practically applicable to asymmetric synthesis. The synthesis of pheromone **1** represents the most efficient synthesis to date (9 steps in longest linear sequence from lactone **3**, 9% overall yield), and the first



Scheme 6 a) **4** (1 equiv), EDC·HCl (15 equiv), HOBt (3 equiv), CH_2Cl_2, 97%; b) TBAF, THF, 78%.

asymmetric synthesis of α-hydroxyacid **4**, avoiding the need for enzymatic resolution at the final stage,[7] or separation of diastereoisomers after amide bond formation with the serinolipid **5**.[6] We are currently investigating further reactions of the chiral glycolate equivalents **2** and **3** and their application to natural product synthesis.

Acknowledgment

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References

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(3) Asai, N.; Fusetani, N.; Matsunaga, S.; Sasaki, J. *Tetrahedron* **2000**, *56*, 9895.
(4) Loukaci, A.; Bultel-Ponce, V.; Longeon, A.; Guyot, M. *J. Nat. Prod.* **2000**, *63*, 799.
(5) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176.
(6) Asai, N.; Fusetani, N.; Matsunaga, S. *J. Nat. Prod.* **2001**, *64*, 1210.
(7) Masuda, Y.; Yoshida, M.; Mori, K. *Biosci., Biotechnol., Biochem.* **2002**, *66*, 1531.
(8) (a) Diez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem. Int. Ed.* **2001**, *40*, 2906. (b) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett.* **2001**, *3*, 3749. (c) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 4763. (d) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753. (e) Dixon, D. J.; Guarna, A.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synthesis* **2002**, 1973. (f) Ley, S. V.; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608. (g) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Palomero, M. A.; Polara, A.; Rodriguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3618. (h) Michel, P.; Ley, S. V. *Synthesis* **2003**, 1598.
(9) (a) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synlett* **2003**, 1186. (b) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717.
(10) Laib, T.; Chastanet, J.; Zhu, J. P. *J. Org. Chem.* **1998**, *63*, 1709.
(11) Sandri, J.; Viala, J. *Synth. Commun.* **1992**, *22*, 2945.

(12) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.
(13) The X-ray structural data for this compound have been deposited with the Cambridge Crystallographic Data Centre, reference number CCDC 257805. These data can be obtained free of charge on the web at www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.
(14) Koskinen, A. M. P.; Chen, J. S. *Tetrahedron Lett.* **1991**, *32*, 6977.
(15) Masaki, Y.; Yoshizawa, K.; Itoh, A. *Tetrahedron Lett.* **1996**, *37*, 9321.
(16) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.
(17) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989.
(18) Physical data for pheromone **1**, (2*S*,2′*R*,3*S*,4*S*)-2-(2′-hydroxy-21′-methyl-docosanoylamino)-1,3,4-pentadecanetriol: $[\alpha]_D^{22}$ +12.5 (*c* 0.16, $CHCl_3$–MeOH, 1:1) {lit. $[\alpha]_D^{28}$ +14 (*c* 0.70, $CHCl_3$–MeOH, 1:1), see ref.[7]}. IR (film): ν_{max} = 3377 (O-H, N-H), 2917 (C-H), 2850 (C-H), 2480, 1639 (C=O), 1620, 1471, 1049 (C-O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$–CD_3OD, 1:1): δ = 0.82 [6 H, d, *J* = 6.6 Hz, $CH(CH_3)_2$], 0.85 (3 H, t, *J* = 6.6 Hz, CH_3), 1.06–1.60 [55 H, br m, 27 × CH_2, $CH(CH_3)_2$], 1.60–1.69 (1 H, m, H-5), 1.70–1.80 (1 H, m, H-5), 3.50–3.53 (2 H, m, H-4, H-2′), 3.71 (1 H, dd, *J* = 11.3, 4.8 Hz, H-1), 3.76 (1 H, dd, *J* = 11.3, 4.8 Hz, H-1), 4.00 (1 H, dd, *J* = 7.7, 3.7 Hz, H-3), 4.06–4.10 (1 H, m, H-2). ^{13}C NMR (125 MHz, $CDCl_3$–CD_3OD, 1:1): δ = 13.10, 21.70, 22.00, 24.50, 25.20, 26.80, 27.30, 28.70, 28.88, 28.93, 29.01, 29.03, 29.10, 29.12, 29.30, 31.30, 31.90, 33.90, 38.40, 50.90, 60.30, 71.20, 71.60, 74.60, 175.17. Found (ES): $[M - Na]^+$ 650.5729, $C_{38}H_{77}NO_5$ requires 650.5694.