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Synthetic Studies towards Amphidinolide A. A Concise Synthesis of the Unique Ene-Tetrol Unit from a Methyl α-D-Glucopyranoside

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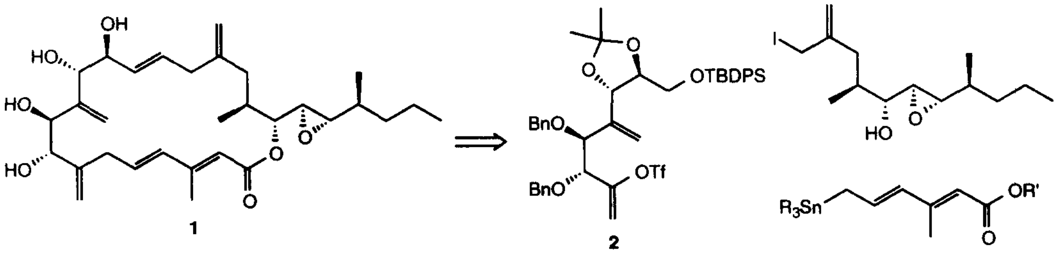
Abstract: A synthesis of the protected ene-tetrol unit **2** present in the marine metabolite amphidinolide A **1**, starting from the protected D-glucopyranoside **3**, and proceeding *via* the key intermediates **4**, **5**, **6** and **7** is described. © 1998 Elsevier Science Ltd. All rights reserved.

The amphidinolides are marine natural products produced by dinoflagellates of the genus *Amphidium*.[1,2] Several of their number show pronounced toxicity against various tumor cell lines.[1] Amphidinolide A **1** was the first of the series to be isolated and characterised.[3] The compound shows a structure based on a 20-membered macrolactone which incorporates three *exo*-methylene groups and four uniquely positioned hydroxy groups forming a hydrophilic sector in the molecule. As a result of our interests in developing the scope for Pd(0)-mediated carbon-to-carbon coupling reactions in macrocycle constructions, we have earlier described a strategy to the polyene macrolactone core in amphidinolide A involving the sp^2-(vinyl)-sp^3-(alkyl) intramolecular coupling sequence depicted in the retrosynthetic analysis shown in Scheme 1.[4] In further studies towards a total synthesis of **1**,[5] we now describe a concise synthesis of the novel ene-tetrol portion **2** appropriately functionalised for later elaboration, by suitable sp^2-sp^3 coupling reactions, to the target natural product.



Scheme 1

Consideration of the high concentration of stereodefined hydroxy functionality in the fragment **2** suggested that a suitable derivative of D-glucose would make an ideal starting material; such a compound is available in the protected methyl α-D-glucopyranoside **3** which is a known compound.[6] The plan was to convert this precursor into the aldehyde **5** *via* the alkene **4**, then introduce the second extra carbon by addition to the aldehyde function in **5**, leading to **6**, and finally open the ring in the pyranoside **6** to reveal the acyclic tetrol precursor **7**.

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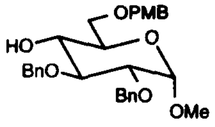

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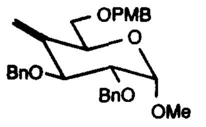

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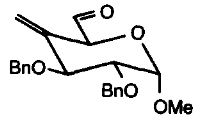

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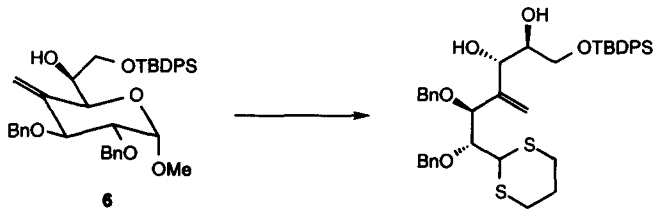

6

7

Thus, oxidation of the glucopyranoside 3[6] under Swern conditions first gave the ketone 8[7] which was then converted into the corresponding alkene 4 in 90% yield on treatment with the "Lombardo reagent"[8] produced from dibromomethane, zinc dust and titanium tetrachloride (Scheme 2). The *p*-methoxybenzyl group protection in 4 was next removed selectively using ceric ammonium nitrate,[6] and the resulting alcohol 9 was then smoothly oxidised under Swern conditions leading to the β,γ-unsaturated aldehyde 5. We then needed a synthetic equivalent of the $-CH_2OH$ synthon to add to 5 in order to elaborate 11 in a diastereospecific manner. This was achieved using the Grignard reagent derived from (chloromethyl)dimethyl(phenylthiomethyl)silane, first developed by van Boom and co-workers.[9] Thus treatment of 5 with this Grignard reagent gave rise to the silyl alcohol 10, as a single diastereoisomer, in 68% yield. Oxidative cleavage of the carbon-to-silicon bond in 10, using hydrogen peroxide in the presence of selenium dioxide under the conditions of Tamao[10] modified by van Boom,[9] then gave the vicinal diol 11 in 73% yield.

The primary hydroxyl group in 11 was next protected as its *t*-butyldiphenylsilyl ether 6, in readiness for the key pyranoside ring opening step. Under optimum conditions, when the pyranoside 6 was treated with propane-1,3-dithiol (4 equivalents) in the presence of boron trifluoride etherate (3 equivalents) at 0°C for 0.5 h[11] a 28% yield of the dithiane 7 could be secured together with 35% recovered pyranoside which could be recycled.[12]

The acyclic precursor 7 was now elaborated to the aldehyde 12 *via* formation of the acetonide and deprotection of the dithiane group; no racemisation of the centre adjacent to the aldehyde function in 12 was observed under the conditions used. Treatment of 12 with methylcerium choride[13] next led to the corresponding secondary alcohol, which was then oxidised to the corresponding ketone 13 in quantitative yield using Dess-Martin periodinane. The synthesis of the vinyl triflate target compound 2 was then completed following treatment of the ketone 13 with lithium diisopropylamide and then with *N*-phenyltrifluoromethanesulphonimide.[14] Further studies are now in progress to complete a synthesis of amphidinolide A by judicious use of appropriate inter- and intra-molecular sp^2-sp^3 coupling reactions involving precursors based on the vinyl triflate 2 and the other intermediates shown in Scheme 1.

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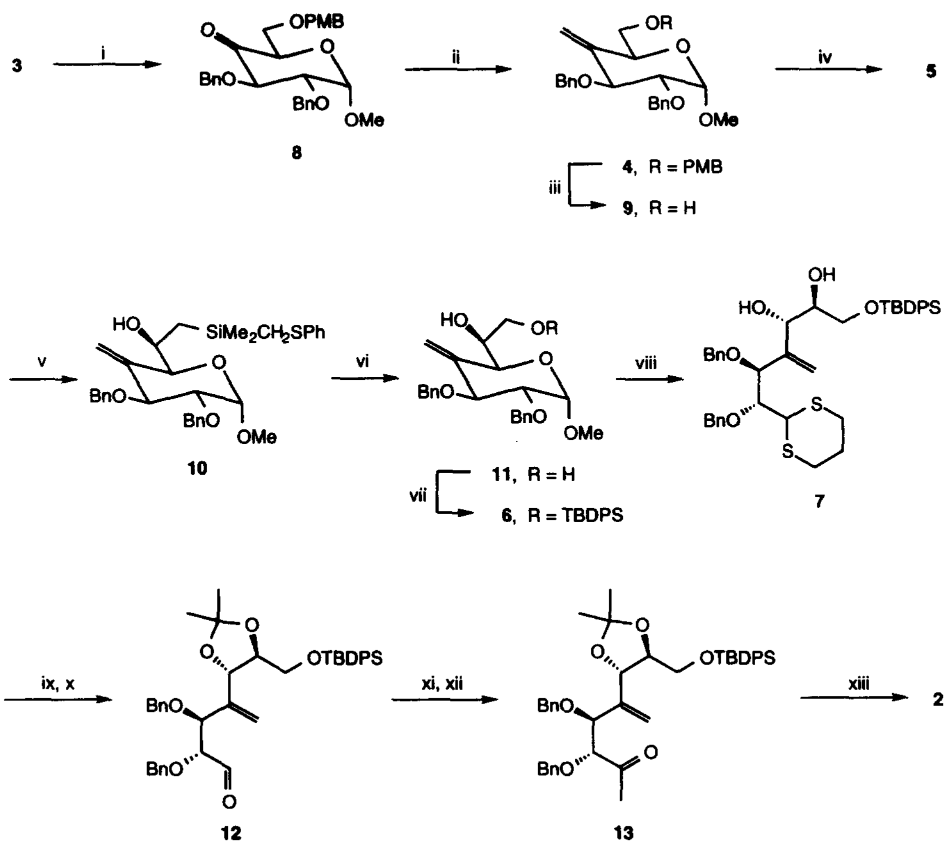

Reagents: i, DMSO, $(COCl)_2$, Et_3N, 95%; ii, Zn, CH_2Br_2, $TiCl_4$, 90%; iii, CAN, 72%; iv, DMSO, $(COCl)_2$, Et_3N, 90%; v, $PhSCH_2SiMe_2CH_2MgCl$, 68%; vi, H_2O_2, SeO_2, $KHCO_3$, KF, 73%; vii, TBDPSCl, Et_3N, DMAP, 83%; viii, $HS(CH_2)_3SH$, $BF_3{\bullet}OEt_2$, 28%; ix, $(MeO)_2CMe_2$, TsOH, 98%; x, MeI, $CaCO_3$, 98%; xi, $MeCeCl_2$, 42%; xii, Dess-Martin periodinane 100%; xiii, LDA, $PhNTf_2$, 82%

Scheme 2

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7. All new compounds showed satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data. Data for **13**: δ_H (400 MHz, $CDCl_3$): 7.75-7.67 (4H, m), 7.45-7.20 (16H, m), 5.62 (1H, s), 5.51 (1H, s), 4.59-4.46 (4H, m), 4.31 (1H, d, *J* = 2.6), 4.19 (1H, d, *J* = 11.6), 3.92 (1H, d, *J* = 3.0), 3.88 (1H, dt, *J* = 8.3, 2.6), 3.83 (1H, dd, *J* = 11.5, 2.7), 3.60 (1H, dd, *J* = 11.5, 3.5), 2.14 (3H, s), 1.47 (3H, s), 1.44 (3H, s), 1.09 (9H, s); δ_C (125 MHz, $CDCl_3$): 210.2 (s), 140.9 (s), 137.6 (s), 137.2 (s), 135.7 (d), 133.1 (s), 133.0 (s), 129.8 (d), 129.7 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.6 (d), 117.4 (t), 108.9 (s), 85.5 (d), 80.8 (d), 79.2 (d), 73.8 (t), 71.4 (t), 62.7 (t), 27.8 (q), 27.1 (q), 27.0 (q), 26.8 (q), 19.3 (s); MS (FAB), *m/z* (%): 701 (M^+ + Na, 9), 197 (10), 135 (23), 91 (100); HRMS, *m/z* for $C_{42}H_{50}O_6SiNa$ (M^+ + Na), calc: 701.3274; found: 701.3233.
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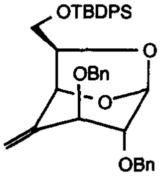
12. Unfortunately, longer reaction times or use of excess boron trifluoride etherate led almost entirely to the anhydro sugar **14**, presumably by way of intramolecular attack of the free hydroxyl group in **6** onto the adjacent oxonium ion intermediate.



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