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Carbohydrate-based routes to salicylate natural products: formal total synthesis of (+)-apicularen A from D-glucal

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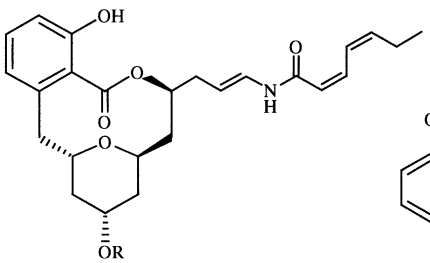
Abstract—A synthesis of apicularen analogue (−)-**4** in 18 steps from D-glucal is reported. As (+)-**4** has been converted into apicularen A in 8 steps, this constitutes a formal total synthesis of this potent naturally occurring anti-cancer agent.

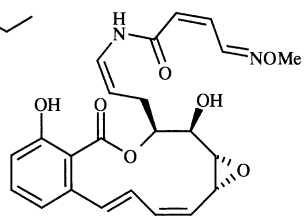
(−)-Apicularen A **1** and (−)-apicularen B **2** are recently discovered[1] members of the rapidly growing family of salicylate anti-tumour natural products. Other members of this family of macrolides include the salicylihalamides discovered in 1997,[2] the lobatamides,[3] CJ-12,950,[4] and the oximidines (e.g. Oximidine I **3**),[5] all of which exhibit high levels of biological activity, notably towards tumour cells.

Jansen et al. reported very high cytostatic activity for apicularen A against nine different human cancer cell lines, including the multi-drug resistant line KB-V1 (IC_{50} values ranging between 0.3 and 3 ng/ml), and the induction of several abnormal effects in tumour cells.[1] In addition, in the 60 cell line tumour screen at the NCI, apicularen A (in common with the salicylihalamides and the lobatamides) exhibited no significant correlation with the profile of any other anti-tumour compound, thus indicating a novel mode of action. As a result, interest in the total synthesis of this novel class of compounds,[6] their analogues[7] and unique enamide side chains[8] has flourished.

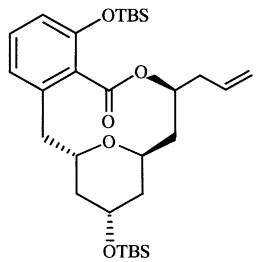
The first total synthesis of (−)-apicularen A, in which the tetrahydropyran unit was constructed via hetero-Diels–Alder chemistry, was recently published by De Brabander et al.[6a,7a] Allyl-substituted macrolide (+)-**4** was a key intermediate in this route, side chain elaboration (eight steps, 4% overall yield) completing the natural product synthesis. This Letter reports the synthesis of (−)-**4** via an alternative carbohydrate-based route, and thus constitutes a formal total synthesis of (+)-apicularen A.



R = H, (−)- apicularen A (**1**)
R = *N*-acetyl-β-glucosamine, (−)- apicularen B (**2**)



oximidine I (**3**)



(+)-**4**

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Our approach to the apicularen nucleus is shown in retrosynthetic form in Fig. 1. We envisaged the use of D-glucal **5** as a chiral building block for the construction of the key apicularen precursor **6**. Pyran **6** is doubly electrophilic and initial cross-coupling with a protected salicylic acid synthon **7** to provide the 9-(arylmethyl)tetrahydropyran **8** followed by elaboration of the anomeric position would furnish hydroxy-acid **9**. Macrolactonisation of **9** should lead to the required 12-membered macrocycle (−)-**4**.

The crucial triflate **6** required for the organometallic coupling step was prepared from D-glucal **5** in a four-step process (Scheme 1). Sequential derivatisation of each hydroxyl in a one-pot procedure gave (thiocarbonyl)imidazolide **10**, which underwent Bu_3SnH-mediated deoxygenation[9] to give dihydropyran **11** in good yield.[10] Acid-catalysed addition of methanol across the enol ether,[11] together with concomitant deprotection of the primary silyloxy group, was effected using triphenylphosphine hydrobromide giving alcohol **12**. Reaction of **12** with triflic anhydride in the presence of pyridine gave the unstable triflate **13**, which was used immediately after chromatographic purification.

The completion of the synthesis of (−)-**4** is shown in Scheme 2. Initial studies were carried out to introduce the 9-aryl-substituent using functionalised Grignard reagents **7**.[12] Unfortunately, success in model studies could not be repeated for the conversion of **13** into adducts related to **16**. After extensive study, Kotsuki's benzofuryl Grignard reagent **14**[13] was found to be the most effective salicylate equivalent for triflate displacement, providing reasonable yields of coupled product **15**. Adduct **15** was oxidatively cleaved with ozone to give aldehyde **16**, and further oxidation, deprotection and methylation provided methyl ester **17**. Lewis acid-mediated allylation of the anomeric methyl acetal was carried out using allyltrimethylsilane to give an excellent yield of a single stereoisomer, presumed to be the α-*C*-glycoside.[14] A significant amount of TPS group cleavage was evident during this process, and the resultant secondary alcohol could not be reprotected using TPSCl. Therefore, complete removal of the TPS group was carried out using fluoride and then treatment with the more reactive silylating agent TBSOTf provided the TBS ether **18** in good yield. Ozonolysis of **18** gave aldehyde **19** which underwent reagent-controlled allyla-

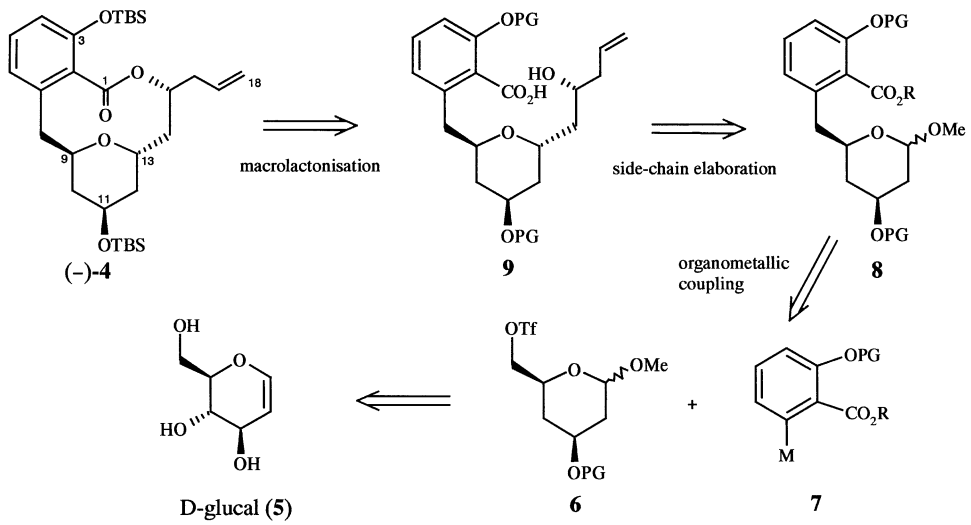
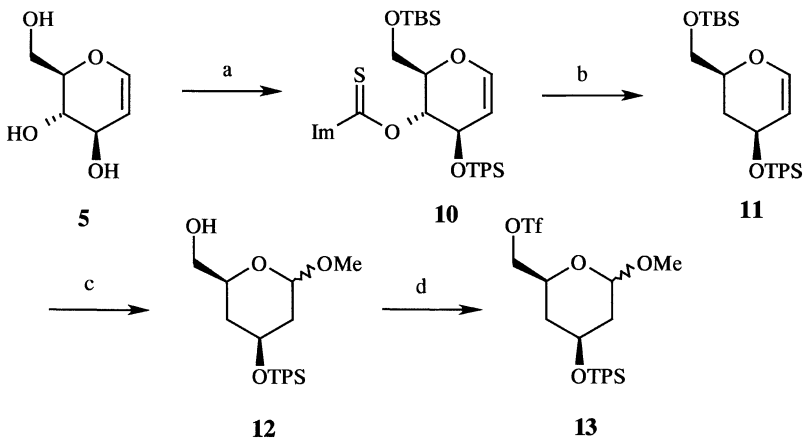
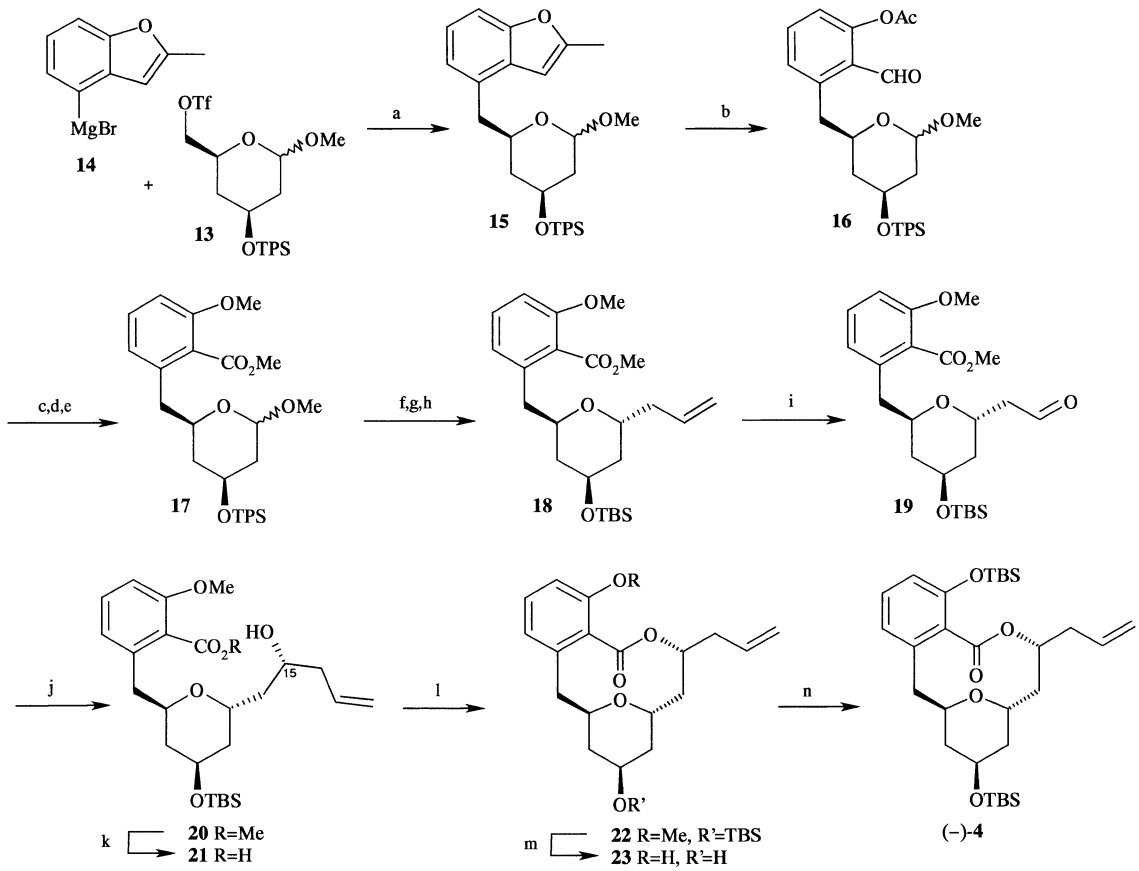


Figure 1.



Scheme 1. *Reagents and conditions*: (a) imidazole, TBSCl, then imidazole, TPSCl, then $(Im)_2CS$ (65%); (b) Bu_3SnH, AIBN, toluene, Δ (85%); (c) $Ph_3P{\cdot}HBr$, MeOH, CH_2Cl_2, 0°C, 16 h (65%); (d) Tf_2O, pyridine, CH_2Cl_2, −12°C, 10 min (96%).



Scheme 2. *Reagents and conditions*: (a) 0.1 equiv. CuBr, THF, 0°C, 14 h (59%); (b) i. O_3, CH_2Cl_2, −78°C, ii. PPh_3, −78°C to rt, 2 h (68%); (c) H_2O_2, $NaClO_2$, $NaHSO_3$, NaH_2PO_4, H_2O, MeCN, 3 h; (d) K_2CO_3, MeOH, 0.5 h; (e) MeI, K_2CO_3, acetone, Δ, 24 h (75%, three steps); (f) TMSOTf, allyltrimethylsilane, MeCN, −78°C; (g) TBAF, THF, 16 h; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (81%, three steps); (i) i. O_3, CH_2Cl_2, −78°C, ii. Ph_3P, −78°C to rt, 3 h (98%); (j) (−)-*B*-allyl-β-(diisopinocampheyl)borane, Et_2O, −78°C (60%); (k) LiI, pyridine, Δ, 24 h (55%; 88% based on r.s.m.); (l) DCC, DMAP, DMAP·HCl, $CHCl_3$, Δ (30%); (m) 9-iodo-9-BBN, CH_2Cl_2, 0°C, 2 h (70%); (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (80%).

tion using Brown's diisopinocampheyl(allyl)borane[15] to supply an inseparable 90:10 mixture of diastereomeric alcohols. The structure of the major isomer **20** was assigned by literature precedent[15] and by Mosher ester studies[16] on the mixture of **20** and its C-15 stereoisomer. Lithium iodide-induced ester cleavage allowed access to hydroxy-acid **21** in good yield.

Macrolactonisation of **21** was successful utilising Keck's protocol[17] and gave a separable mixture of 12-membered lactone **22** in 30% yield {$[\alpha]_D = -6.3$ (*c* 0.5, $CHCl_3$); mp 149–150°C} together with a trace of its C-15 epimer. Deprotection of **22** using 9-iodo-9-BBN[18] gave phenol **23**, which was fully characterised and shown to have comparable analytical/spectroscopic data to that reported by De Brabander et al. {$[\alpha]_D = -4.5$ (*c* 0.15, MeOH); lit. $[\alpha]_D$ for enantiomer $= +6.8$ (*c* 0.16, MeOH)}.[7a,19] Finally, silylation of both hydroxyl groups provided the bis-TBS ether (−)-**4** {$[\alpha]_D = -19.7$ (*c* 0.10, $CHCl_3$)}.

The enantiomeric compound (+)-**4** has been converted into (−)-apicularen in eight steps (4% overall yield) by a published procedure.[6a] The synthetic studies in this Letter therefore constitute a formal total synthesis of (+)-apicularen A. We are currently optimising the route described herein and extending it to other members of the salicylate natural product family.

Acknowledgements

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19. Compound (–)-**23**: Found (CI): 319.15453. $C_{18}H_{22}O_5$ requires [MH^+], 319.15455 (0.1 ppm error); ν_{max}/cm^{-1} (thin film) 3262, 2924, 1716, 1583, 1464, 1294; *m/z* (CI) 319 [MH^+, 100%], 301 (70), 283 (20), 162 (20), 134 (25); ^1H NMR (500 MHz, acetone-D_6) δ 8.39 (1H, s, 3-OH), 7.11 (1H, dd, *J* 8.0, 7.7 Hz, H5), 6.77 (1H, d, *J* 8.0 Hz, H4), 6.69 (1H, d, *J* 7.7 Hz, H6), 5.92 (1H, dddd, *J* 6.4, 7.6, 10.2, 17.2 Hz, H17), 5.48 (1H, dddd, *J* 2.4, 5.6, 5.6, 10.0 Hz, H15), 5.13 (1H, dddd, *J* 1.6, 1.6, 2.4, 17.2 Hz, H18), 5.03 (1 H, dddd, *J* 1.6, 1.6, 2.4, 10.2 Hz, H18′), 4.24–4.30 (1H, m, H13), 3.96–4.03 (1H, m, H11), 3.85–3.91 (1H, m, H9), 3.77–3.81 (1H, m, 11-OH), 3.34 (1H, dd, *J* 9.8, 15.0 Hz, H8), 2.44 (1H, dd, *J* 1.0, 15.0 Hz, H8′), 2.30–2.41 (2H, m, H16/16′), 1.93 (1H, ddd, *J* 4.5, 4.5, 12.7 Hz, H10), 1.77–1.86 (1 H, m, H14), 1.40–1.71 (4H, m, H10′, H14′, H12/12′); ^{13}C NMR (125 MHz, acetone-D_6); δ 169.2, 154.3, 140.2, 135.3, 130.3, 125.5, 122.3, 117.5, 114.4, 73.7, 73.6, 68.1, 64.9, 40.4, 40.1, 40.0, 39.7, 39.1. The ^{13}C NMR data for this compound differ slightly from those published for (+)-**23**.[7a] However, Professor De Brabander has subsequently amended the published data and there is now an extremely good correlation (personal communication, May 2001).