Pergamon

Tetrahedron Letters 41 (2000) 8069–8073

TETRAHEDRON LETTERS

Synthesis of side chain truncated apicularen A

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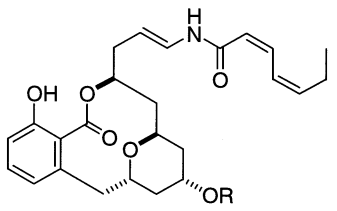
Received 7 August 2000; accepted 17 August 2000

Abstract

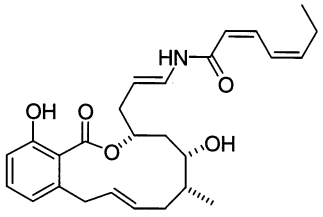
The potent cytostatic agent apicularen A belongs to a growing class of macrocyclic salicylates with unique biological properties. Herein, we present a short enantioselective synthesis of side chain truncated apicularen A.

Keywords: antitumor compounds; natural products; hetero Diels–Alder.

In 1998, Höfle and coworkers reported the isolation of apicularens A and B (**1**–**2**, Fig. 1) from *Chondromyces* sp.[1] and subsequently assigned their relative and absolute configuration.[2] Apicularens structurally relate to the marine-derived salicylihalamides (**3**),[3] the first members of a



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



3 - salicylihalamide A

Figure 1.

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0040-4039/00/$ - see front matter
PII: S0040-4039(00)01403-9

growing class of novel macrocyclic salicylates adorned with an unusual enamide appendage.[4] Interestingly, these biosynthetically unique metabolites are endowed with a combination of structural features that conspire to elicit unique responses in mammalian cells.[1–4] For example, salicylihalamides were reported to have a potentially new mechanism of antineoplastic activity.[3] Phenotypes associated with apicularen A treatment include potent growth inhibition of human cancer cell lines (IC_{50} ~0.1–3 ng/mL), the induction of an apoptotic-like cell death, and the formation of mitotic spindles with multiple spindle poles and clusters of bundled actin from the cytoskeleton.[1,2]

In order to define the molecular basis for these activities, which remains unknown, we initiated a program towards the synthesis of these intriguing natural products, as well as derived probe reagents. In this context, we recently finished the first total synthesis of salicylihalamide A and revised its absolute configuration.[5] Herein, we report an efficient synthesis of side chain truncated apicularen A.[6]

Dihydropyranone **5**, to be derived through hetero-Diels–Alder chemistry, was considered a useful intermediate for the stereoselective construction of the tetrahydropyranyl ring present in target structure **4** (Fig. 2). The conjugate addition of an acetaldehyde synthon (e.g. vinylMgBr) would control stereochemistry at C13 (1,6-*trans* tetrahydropyran) and a reagent-controlled allylation was envisioned for the manipulation of C15 stereochemistry.

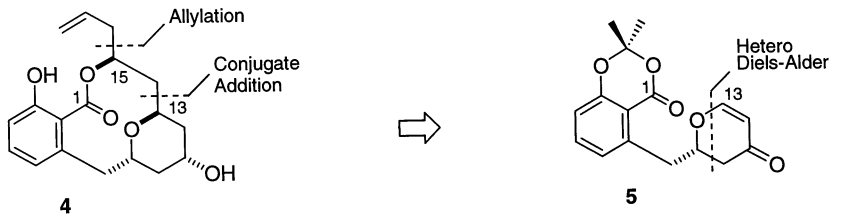
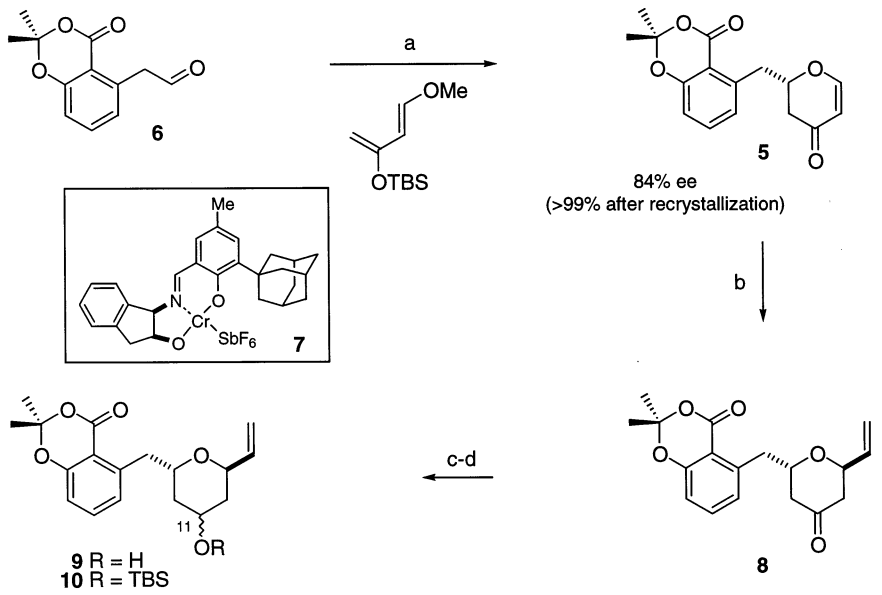


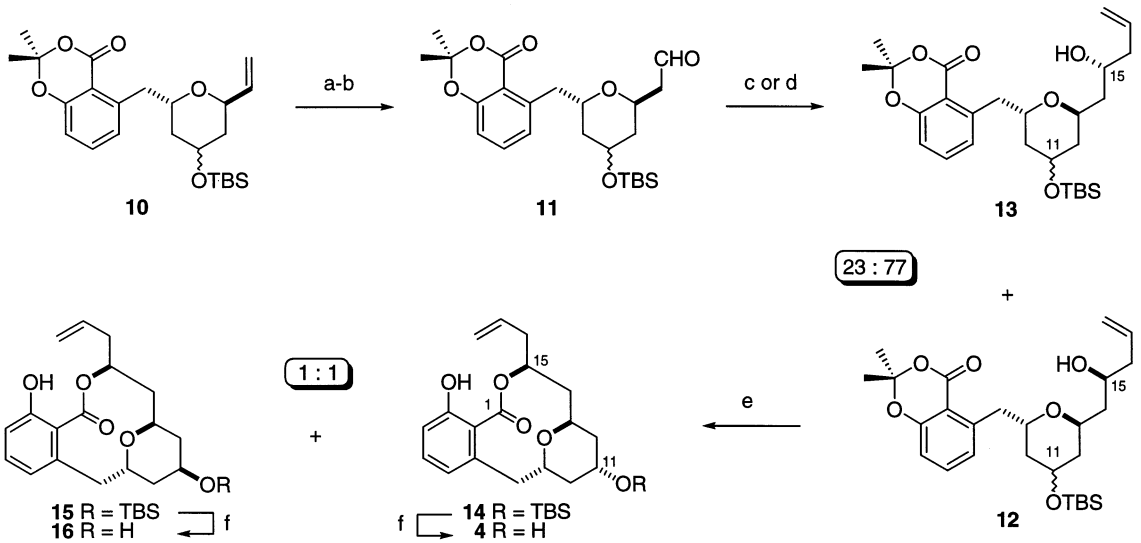
Figure 2. Retrosynthetic analysis

The enantioselective assembly of dihydropyranone **5** involved a (2+4) cycloaddition of aldehyde **6** with Danishefsky's diene[7] catalyzed by Jacobsen's chiral chromium(III)-complex **7** (Scheme 1).[8] After treatment of the intermediate cycloadduct with CF_3CO_2H, the corresponding dihydropyranone **5** was obtained in 84% ee (>99% ee after recrystallization), as determined by analytical HPLC (Chiralcel® OD–H; flow rate: 1 mL/min, 5% ^{i}PrOH/hexanes; t_R major enantiomer = 27.5 min, t_R minor enantiomer = 30.8 min). Proceeding with a copper(I)-catalyzed conjugate addition of vinylmagnesium bromide, 1,6-*trans*-tetrahydropyranone **8** was obtained diastereomerically pure in 78% yield.[9] The next step involved a stereoselective ketone reduction, and a variety of reducing agents were explored. Unfortunately, an inseparable mixture of epimeric alcohols **9** (~1:1) was produced in all cases. This is perhaps not surprising if one considers a Curtin–Hammett situation in which two rapidly equilibrating conformers of tetrahydropyranone **8** (axial vinyl substituted **8** and axial CH_2aryl substituted **8**) react at comparable rates, even so with stereoselective reducing agents. Notwithstanding this drawback, we continued our synthesis and the epimeric alcohol mixture **9** was converted to the corresponding silylether mixture **10**.



Scheme 1. Reagents and conditions: (a) cat. **7**, 4 Å molecular sieves, acetone, rt, 24 h; then CF_3CO_2H, CH_2Cl_2, 0°C, 1 h (60%); (b) vinylMgBr, CuI, DMPU, TMSCl, −78°C, 3 h→−40°C, 1 h (78%); (c) $NaBH_4$, MeOH (99%); (d) TBSCl, imidazole, cat. DMAP, DMF (99%)

Having secured the requisite tetrahydropyranyl ring-system, the latent C15–aldehyde **11** was unmasked via a hydroboration/peroxide treatment and oxidation of the resulting primary alcohol with tetrapropylammonium perruthenate[10] (Scheme 2). Completion of the macrocyclic portion of apicularen A entailed an allylation/lactonization sequence. Given the intrinsic facial bias of β-alkoxy aldehydes for 1,3-*anti* addition products,[11] we initially opted for a reagent-con-



Scheme 2. Reagents and conditions: (a) BH_3·THF, THF; then aq. H_2O_2, aq. NaOH (65%); (b) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2 (67%); (c) allylB^dIpc$_2$, Et_2O, −78°C (65%); (d) AllylTMS, $TiCl_4$, CH_2Cl_2, −78°C (72%); (e) NaH, THF (70%); (f) amberlyst-15, MeOH (99%)

trolled allylation of aldehyde **11** with Brown's *B*-allyldiisopinocampheylborane,[12] which delivered a 77:23 mixture of diastereomeric homoallyl alcohols **12** and **13** in a mismatched double diastereodifferentiating reaction. We subsequently found however, that the use of allyltrimethylsilane (1 equiv. of $TiCl_4$, CH_2Cl_2, −78°C) produced an identical mixture (**12**:**13** = 77:23) but in a slightly better yield (72%).[13]

Stirring a solution of homoallyl alcohol **12** (mixture of C11-epimers) in the presence of NaH effected the crucial lactonization event, delivering lactones **14** and **15** in 70% yield. After protecting group removal, preparative TLC (20% EtOAc/CH_2Cl_2) finally allowed the separation of the corresponding C11-epimeric alcohols **4** and **16**.[14] The chemical shift values and coupling constants of protons H8 through H15 of truncated apicularen **4** are nearly identical to the values reported for apicularen A,[2] confirming its relative configuration. Epimer **16** on the contrary, produces an NMR-profile significantly different from the natural product.

In summary, we have synthesized a truncated version of apicularen A in nine linear steps from aldehyde **6**. NMR spectroscopic evaluation of **4** indicates that it adopts a similar conformation in solution than the macrocyclic portion of apicularen A. We are currently evaluating the cell-growth inhibitory potential of **4** and **16** as well as progressing towards a total synthesis. These results will be reported in due course.

Acknowledgements

Financial support provided by the Robert A. Welch Foundation and junior faculty awards administered through the Howard Hughes Medical Institute and the University of Texas Southwestern Medical Center are gratefully acknowledged. We thank Yao Hain Ing (Schering Plough Research Corporation) for providing high-resolution mass spectroscopy data.

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14. Compound **4**: $[\alpha]_D = +6.8$ (MeOH, *c* 0.16); IR 3262, 2924, 1711, 1584, 1463, 1288, 1085, 755 cm^{-1}; ^1H NMR (400 MHz, acetone-D_6) δ 8.36 (1H, s), 7.11 (1H, dd, $J = 7.6$, 8.0 Hz), 6.77 (1H, d, $J = 8.0$ Hz), 6.70 (1H, d, $J = 7.6$ Hz), 5.92 (1H, dddd, $J = 6.4$, 7.6, 10.4, 17.6 Hz), 5.48 (1H, dddd, $J = 2.4$, 5.6, 5.6, 10.0 Hz), 5.14 (1H, dddd, $J = 1.6$, 1.6, 2.4, 17.6 Hz), 5.03 (1H, dddd, $J = 1.6$, 1.6, 2.4, 10.4 Hz), 4.27 (1H, dddd, $J = 2.0$, 5.0, 7.0, 10.8 Hz), 3.99 (1H, ddddd, $J = 4.0$, 4.1, 5.1, 7.6, 8.8 Hz), 3.88 (1H, dddd, $J = 1.2$, 4.8, 8.0, 10.0 Hz), 3.77 (1H, d, $J = 4.0$ Hz), 3.34 (1H, dd, $J = 9.6$, 15.2 Hz), 2.44 (1H, dd, $J = 1.6$, 15.2 Hz), 2.28–2.44 (2H, m), 1.93 (1H, ddd, $J = 4.8$, 4.8, 12.8 Hz), 1.83 (1H, ddd, $J = 10.8$, 10.8, 14.4 Hz), 1.68 (1H, ddd, $J = 5.2$, 7.2, 12.8 Hz), 1.58 (1H, ddd, $J = 2.0$, 2.4, 14.4 Hz), 1.52 (1H, ddd, $J = 4.4$, 7.2, 12.8 Hz), 1.49 (1H, ddd, $J = 8.4$, 8.4, 12.8 Hz); ^{13}C NMR (75 MHz, acetone-D_6) δ 169.8, 161.2, 154.8, 140.1, 135.9, 130.8, 122.9, 118.0, 114.9, 74.2, 74.1, 68.6, 65.4, 40.9, 40.6, 40.5, 40.3, 39.6; MS (CI) 318 [M^+], 301, 283, 251, 231, 207, 163, 134, 97, 94. Compound **16**: ^1H NMR (400 MHz, acetone-D_6) δ 8.40 (1H, s), 7.14 (1H, dd, $J = 7.6$, 8.0 Hz), 6.79 (1H, d, $J = 8.0$ Hz), 6.76 (1H, d, $J = 7.6$ Hz), 5.91 (1H, dddd, $J = 7.2$, 7.2, 10.4, 17.2 Hz), 5.50 (1H, dddd, $J = 4.0$, 5.6, 7.2, 10.0 Hz), 5.14 (1H, dddd, $J = 1.6$, 1.6, 2.0, 17.2 Hz), 5.04 (1H, dddd, $J = 1.2$, 1.2, 2.0, 10.4 Hz), 3.97–4.04 (1H, m, $\Delta J = 24.8$ Hz), 3.87–3.96 (2H, m), 3.73 (1H, d, $J = 4.8$ Hz), 3.32 (1H, dd, $J = 11.6$, 14.0 Hz), 2.33–2.38 (2H, m), 2.34 (1H, dd, $J = 1.6$, 14.0 Hz), 1.67–1.91 (4H, m), 1.64 (1H, ddd, $J = 6.4$, 9.6, 13.2 Hz), 1.20 (1H, ddd, $J = 9.2$, 10.8, 12.4 Hz); ^{13}C NMR (75 MHz, acetone-D_6) δ 171.0, 154.4, 141.3, 135.8, 131.0, 126.4, 122.8, 118.0, 114.9, 76.3, 74.4, 68.8, 66.0, 42.5, 41.8, 40.2, 40.0, 37.6.