Synthesis of side chain truncated apicularen A

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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. © 2000 Elsevier Science Ltd. All rights reserved.

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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

Figure 1.

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growing class of novel macrocyclic salicylates adorned with an unusual enamide appendage. Interestingly, these biosynthetically unique metabolites are endowed with a combination of structural features that conspire to elicit unique responses in mammalian cells. For example, salicylihalamides were reported to have a potentially new mechanism of antineoplastic activity. Phenotypes associated with apicularen A treatment include potent growth inhibition of human cancer cell lines (IC<sub>50</sub> ~ 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.

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. Herein, we report an efficient synthesis of side chain truncated apicularen A.

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.

The enantioselective assembly of dihydropyranone 5 involved a (2+4) cycloaddition of aldehyde 6 with Danishefsky’s diene<sup>7</sup> catalyzed by Jacobsen’s chiral chromium(III)-complex 7 (Scheme 1). After treatment of the intermediate cycloadduct with CF<sub>3</sub>CO<sub>2</sub>H, the corresponding dihydropyranone 5 was obtained in 84% ee (>99% ee after recrystallization), as determined by analytical HPLC (Chiralcel<sup>®</sup> OD–H; flow rate: 1 mL/min, 5% iPrOH/hexanes; <i>t</i><sub>R</sub> major enantiomer = 27.5 min, 〈<i>t</i><sub>R</sub> 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. 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<sub>2</sub>aryl 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 silyl ether mixture 10.
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 perruthenate10 (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-
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 TiCl4, CH2Cl2, −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:CH2Cl2) 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.

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References


13. This result was unexpected in light of the usually observed chelation-controlled anti-addition product with TiCl₄ as the Lewis acid; see for example: Reetz, M. T.; Jung, A. J. Am. Chem. Soc. 1983, 105, 4833–4835; Keck, G. E.; Castellino, S. ibid. 1986, 108, 3847–3849. On the contrary, reaction of aldehyde 11 with allyltrimethylsilane in the presence of BF₃·Et₂O or SnCl₄ as Lewis acids gave primarily the expected anti-diastereomer (anti:syn > 95:5).

14. Compound 4: [α]D = +6.8 (MeOH, c 0.16); IR 3262, 2924, 1711, 1584, 1463, 1288, 1085, 755 cm⁻¹; ¹H NMR (400 MHz, acetone-D₆) 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 = 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); ¹³C NMR (75 MHz, acetone-D₆) 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 (Cl) 318 [M⁺], 301, 283, 251, 231, 207, 163, 134, 97, 94. Compound 16: ¹H NMR (400 MHz, acetone-D₆) 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, ΔJ = 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); ¹³C NMR (75 MHz, acetone-D₆) 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.