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ORGANOZIRCONOCENE-MEDIATED POLYENE SYNTHESIS: PREPARATION OF ASUKAMYCIN AND MANUMYCIN A SIDE CHAINS

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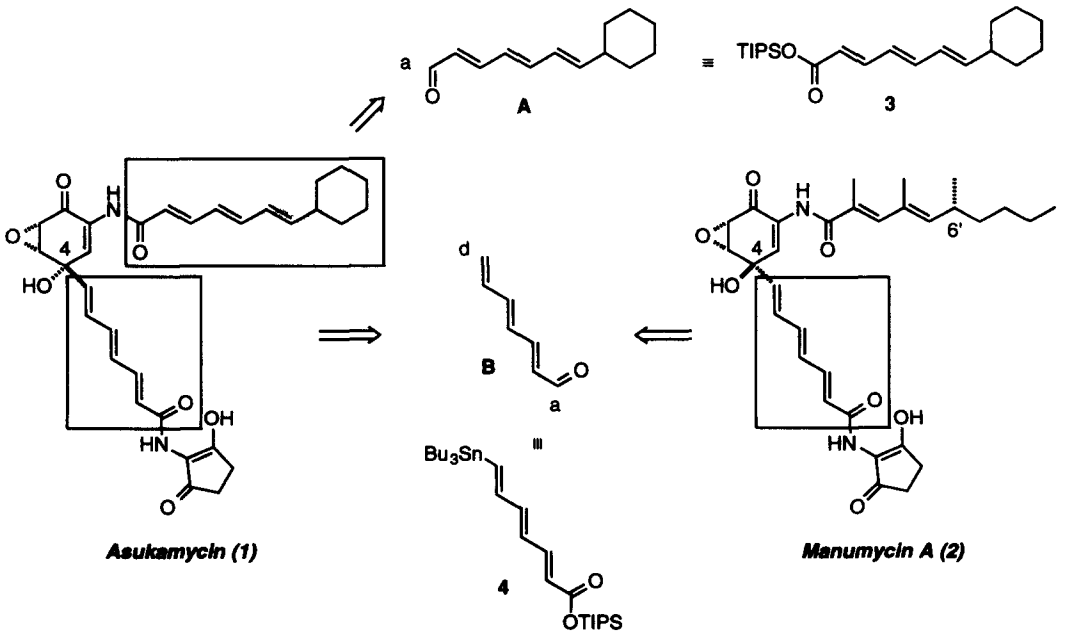
Abstract: Hydrozirconation of a functionalized alkyne followed by transmetalation and 1,2-addition to α,β-unsaturated aldehydes was used for the syntheses of the eastern side chain of asukamycin and a precursor to the southern side chain common to asukamycin and manumycin A. These routes facilitate analog preparation, and the convergent zirconocene strategy represents an alternative to stepwise Wittig condensations or Stille couplings in polyene synthesis. © 1997 Elsevier Science Ltd.

Asukamycin (**1**)[1] and manumycin A (**2**)[2] are members of the manumycin family of antibiotics, which also include alisamycin,[3] nisamycin,[4] and other *Streptomyces* metabolites such as LL-C10037α.[5] In addition to its antibiotic activity, manumycin A is active against fungi and L-1210 leukemia stem cells[6] and has been reported to inhibit leukocyte elastase and Ras farnesyl-transferase.[7] Asukamycin and manumycin have a highly functionalized epoxyquinol core, originating from the condensation of succinyl-CoA and dihydroxyacetone.[8] Attached to this core at the C-2 amino substituent is a polyunsaturated eastern side chain. The southern side chain which is common to asukamycin and manumycin A is composed of a trienyl acid terminated by a 2-amino-3-hydroxycyclopent-2-enone (C_5N) unit.



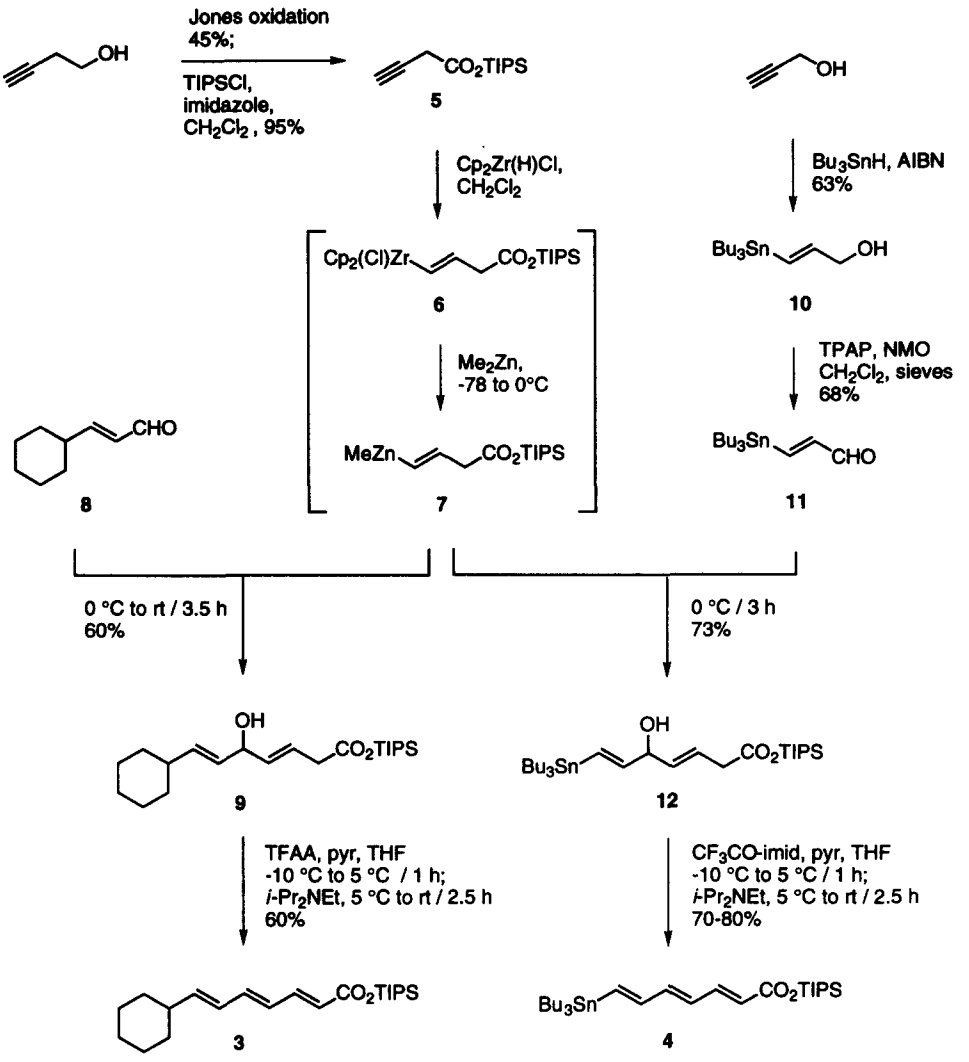
Recently, we employed the Zr→Zn transmetalation methodology in the synthesis of the eastern side chain of manumycin A.[9] This strategy,[10,11] which involves a hydrozirconation, transmetalation and 1,2-addition sequence, has now been applied to the synthesis of trienoate **3**, which may be readily coupled with the amine donor site of the core to establish the top half of asukamycin. A further extension of this convergent protocol which circumvents stepwise Wittig condensations provides **4**, a synthetic equivalent of the a^1, d^7 synthon **B** comprising the trienylacyl unit of the southern sidechains of asukamycin and manumycin A.

Starting with commercially available 3-butyn-1-ol, Jones oxidation[12] (45%) followed by treatment of the resulting acid with imidazole (1 equiv) and TIPSCl (1 equiv) in CH_2Cl_2 gave the TIPS-ester **5** and a small amount of the isomeric allenyl ester (≤ 5%, ^{1}H NMR) as a mixture in 95% yield (Scheme 1).[13] The use of Et_3N in place of imidazole, or elution of the crude reaction mixture through silica gel, increased the isomerization to the allenyl ester to a significant degree. Addition of **5** to a suspension of Schwartz reagent ($Cp_2Zr(H)Cl$)[14] in CH_2Cl_2 while maintaining the reaction temperature near 20 °C resulted in the formation of the alkenylzirconium intermediate **6**.[15] Transmetalation (Me_2Zn)[10] provided the corresponding alkenylzinc species **7**, which subsequently underwent 1,2-addition to the aldehyde **8**[16] to give bis allylic alcohol **9** in 60% yield. Activation of the 2° alcohol function as the trifluoroacetate and base-mediated 1,4-elimination gave all *trans*-trienyl ester **3** as a single stereoisomer (^{1}H NMR) in 60% yield.[17] The (2*E*,4*E*,6*E*)-configuration of the double bonds was assigned on the basis of the vicinal coupling constants of the vinyl protons (15 Hz).

An analogous route was employed in the preparation of the southern side chain unit **4**. Hydrostannylation[18] (63% yield) of 2-propyn-1-ol, followed by TPAP oxidation[19] of the resulting stannyl alcohol **10** provided the aldehyde **11** in 68% yield. Addition of **11** to a cooled (0 °C) solution of **7** gave the bis allylic alcohol **12** in 73% yield. Conversion of **12** to the trifluoroacetate employing 1-(trifluoroacetyl)imidazole (which proved superior to the use of TFAA), followed by base-mediated 1,4-elimination, gave the all *trans*-trienyl stannane **4** as a single stereoisomer (^{1}H NMR) in 70-80% yield. The stannane was unstable on silica gel and thus rapid chromatography after the aqueous workup was critical to obtaining satisfactory yields.[20] The (2*E*,4*E*,6*E*)-configuration of the three double bonds was assigned on the basis of the vicinal coupling constants of the vinyl protons (15 and 18.5 Hz).

In summary, we have employed a one-pot hydrozirconation-transmetalation-1,2-addition sequence followed by a stereoselective 1,4-elimination reaction in the synthesis of the eastern sidechain of asukamycin and in the preparation of a precursor to the southern sidechain of both asukamycin and manumycin A. In contrast to sequential Wittig reactions that are traditionally used for the preparation of these polyenes in natural product synthesis,[21] the zirconocene protocol is more convergent, faster, and more readily amenable to analog synthesis. This organometallic strategy also offers an attractive alternative to polyene syntheses using Pd-mediated $C(sp^2)$-$C(sp^2)$-coupling strategies such as those developed by Stille, Suzuki and Negishi.[22]

Scheme 1



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    To a cooled (-10°C) solution of **12** (426 mg, 0.725 mmol; water was removed from **12** by azeotropic distillation with toluene) in dry THF was added CF_3CO-imidazole (357 mg, 2.18 mmol), followed by pyridine (201 mg, 2.54 mmol). The mixture was allowed to warm to 5 °C over 1 h. Diisopropylethylamine (469 mg, 3.63 mmol) was added and the reaction mixture was allowed to warm to ~15°C over a 2.5 h period. The solution was transferred to a separatory funnel containing water (80 mL) and Et_2O (80 mL). The layers were separated and the organic layer was washed sequentially with sat. aq NH_4Cl (2 × 80 mL), water (80 mL) and brine (80 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude material by column chromatography (30 g of silica gel, 96:4 hexanes-ethyl acetate) afforded 310 mg (75%) of **4** as a yellow-brown oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 0.75-1.05 (m, 15 H), 1.17 (d, 18 H, J = 7.5 Hz), 1.25-1.75 (m, 15 H), 5.90-6.05 (m, 2 H), 6.25 (dd, 1 H, J = 10, 15 Hz), 6.46 (d, 1 H, J = 18.5 Hz), 6.66 (dd, 1 H, J = 10, 18.5 Hz), 7.51 (dd, 1 H, J = 11.5, 15 Hz).
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