

A Concise Synthesis of the C(9)–C(17) Fragment of the Avermectins

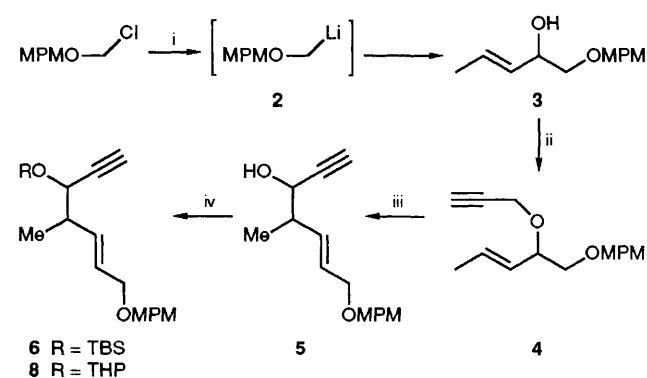
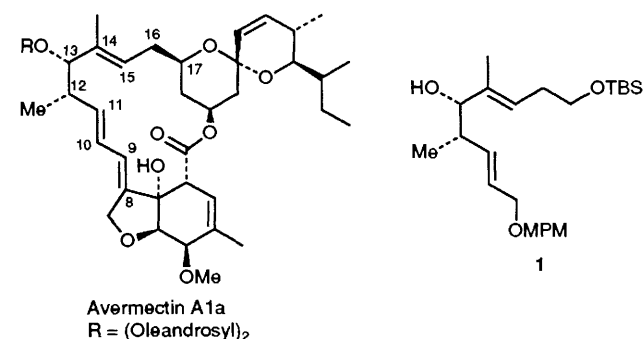
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A rapid entry into the C(9)–C(17) fragment of the avermectins is described which uses a [2,3] sigmatropic rearrangement of a functionalised allylic ether as the key step.

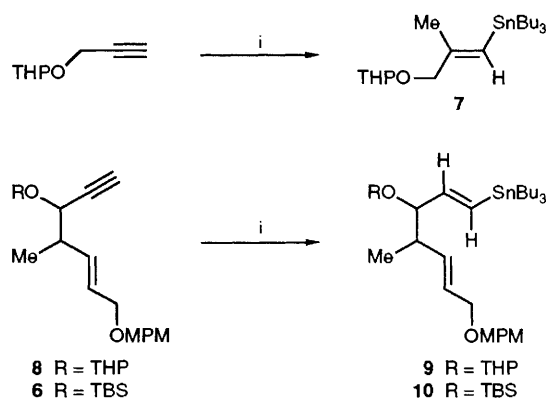
In connection with our continuing study¹ towards the total synthesis of the avermectins, we required a simple and flexible synthetic route to the C(9)–C(17) fragment **1**. We now report our initial findings which are based on the use of the [2,3] sigmatropic or Wittig rearrangement of allylic ethers.²

Formation of 4-methoxybenzyloxymethyl lithium (MPMOCH₂Li) **2** from the corresponding chloromethyl ether,³ according to the procedure of Corey,⁴ followed by addition of crotonaldehyde, gave the allylic alcohol **3** in 60% yield (Scheme 1). Alkylation of **3** with prop-2-ynyl bromide in 1,2-dimethoxyethane (DME) gave the corresponding ether **4** in 81% yield. The [2,3] Wittig sigmatropic rearrangement of the highly *threo*-selective propynyl ether² on treatment with 2.5 equiv. of BuⁿLi in diethyl ether furnished the alcohol **5** as a 6:1 mixture of diastereoisomers. Protection of the hydroxy group using *tert*-butyldimethylsilyl trifluoromethanesulfonate gave the silyl ether **6** in 99% yield. Functionalisation of the acetylenic moiety in **6** was initially investigated by adopting a carbometallation strategy. However, attempts to functionalise **6** with a variety of methyl-copper and cuprate reagents⁵ failed, yielding only recovered starting materials. Similar results were obtained using the trimethylaluminium–cyclopentadienylzirconium dichloride carbometallation method developed by Negishi.⁶

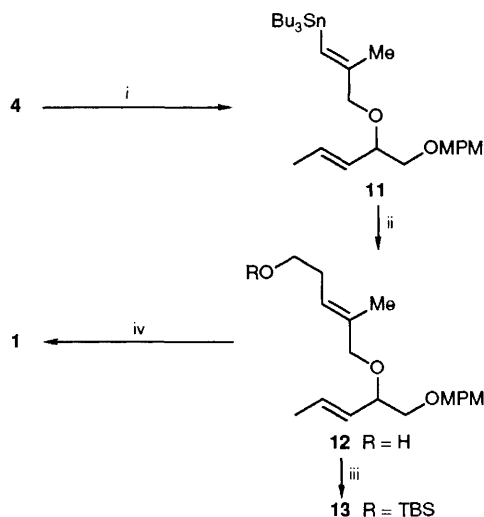


Scheme 1 Reagents: i, SnCl₂, LiBr 0 °C then BuⁿLi -78 °C then MeCH=CHCHO; ii, NaH, NaI, prop-2-ynyl bromide, DME; iii, BuⁿLi, Et₂O, -98 °C; iv, CF₃SO₃SiMe₂Bu^t, 2,6-lutidine, CH₂Cl₂ for **6** or dihydropyran, *p*-MeC₆H₄SO₃H for **8**; (TBS = *tert*-butyldimethylsilyl)

We had previously found that treatment of tetrahydropyran-2-yl (THP) protected propynyl alcohols with the mixed higher order trialkyltin cuprate developed by Lipshutz⁷ and subsequent quenching of the intermediate alkenyl cuprate with methyl iodide gave the vinyl stannane **7** in 81% yield. Thus, protection of the alcohol **5** as its THP derivative (**8**) and treatment of the resulting ether **8** with the stannyl cuprate gave the *trans*-vinyl-stannane **9** in quantitative yield. However, all attempts to methylate the intermediate alkenyl cuprate failed. Similar results were obtained with the silyl protected propynyl alcohol **6** which yielded the vinyl stannane **10** (82%) on attempted methylation with methyl iodide (Scheme 2). Although rather disappointing, these initial results do illustrate the higher reactivity of stannyl cuprates compared with the carbon analogues.



Scheme 2 Reagents: i, BuⁿLi (2 equiv.), CuCN, Bu₃SnH (2 equiv.), tetrahydrofuran (THF), -78 °C, then MeI (excess)



Scheme 3 Reagents: i, BuⁿLi (2 equiv.), CuCN, Bu₃SnH (2 equiv.), THF, -78 °C then MeI; ii, BuⁿLi, THF, -78 °C, then Pr-C≡C-Cu, then ethylene oxide; iii, TBSCl, Et₃N, dimethylformamide (DMF); iv, BuⁿLi–BuⁿOK, THF, hexamethylphosphoric triamide, -116 °C

The alkylation problems were overcome by treating the propynyl ether **4** with the stannyl cuprate and quenching of the intermediate alkenyl cuprate with methyl iodide to give the stannane **11** in 89% yield (Scheme 3). Several methods were investigated for converting **11** to the required alcohol **12**. Direct ligand exchange⁸ with the higher order cuprate derived from methyl lithium and copper cyanide and subsequent treatment with ethylene oxide gave **12** in 48% yield. Alternatively transmetalation of **11** with BuⁿLi then treatment with 2-thienyl(cyano)copperlithium⁹ and reaction of the resulting mixed higher order vinyl cuprate with ethylene oxide catalysed by boron trifluoride–diethyl ether gave **12** in 38% yield.

However, the most convenient method for large-scale preparation was transmetalation, addition of pent-1-ynylcopper(I),¹⁰ and reaction of the resulting mixed cuprate¹¹ with ethylene oxide to give **12** in comparable yields. Protection of **12** with TBSCl gave the silyl ether **13** in 85% yield. We were now at the stage where we could complete the synthesis of **1** by subjecting **13** to the [2,3] sigmatropic rearrangement. Thus, after much experimentation it was found that treatment of **13** with a 3 : 4 mixture of Bu^tLi–Bu^tOK¹² at low temperature gave the desired *threo*-isomer **1** in 44% yield as a single diastereoisomer (Scheme 3).

With these results in hand we are now working on the production of multigram quantities of optically pure **1** via oxidation–chiral reduction of the alcohol **3**. All new compounds have satisfactory analytical and spectral data.

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