

## SYNTHESIS OF THE C11-C28 SUBUNIT OF THE AVERMECTINS

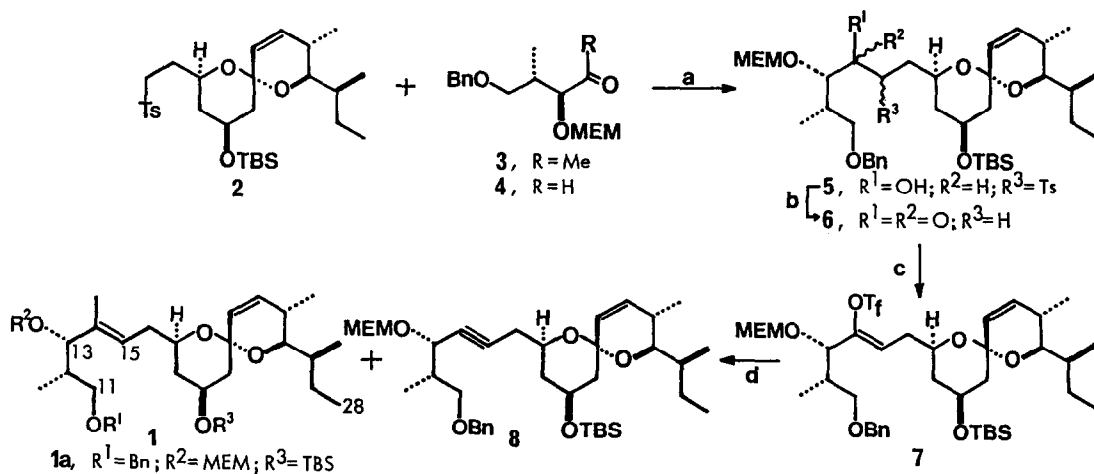
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**Summary:** Construction of the trisubstituted double bond of the C11-C28 subunit of avermectin A<sub>1a</sub> and B<sub>1a</sub> has been achieved in a five-step sequence.

Although several synthetic routes to the spiroacetal (C11-C26) subunit of the milbemycins have been developed,<sup>1)</sup> unexpected difficulty may arise when they are applied to the corresponding subunit (1) of the avermectins because of the presence of an additional C13 oxygen functionality in the latter. So far only one report by Hanessian<sup>2)</sup> has recorded a successful construction of the whole subunit (1).<sup>3)</sup> Here we present an alternative approach to it.<sup>4)</sup>

Our first attempt to extend the Julia-Kocienski procedure<sup>5)</sup> to the trisubstituted olefin synthesis<sup>2)</sup> failed, because the condensation of the lithium anion of sulfone 2<sup>3a)</sup> with ketone 3<sup>6)</sup> resulted in their complete recovery.<sup>7)</sup> However, the coupling of 2 with aldehyde 4<sup>6)</sup> was found to proceed quantitatively to give a diastereomeric mixture of 5. Therefore, we turned to the stereoselective olefin synthesis according to McMurry's procedure.<sup>8)</sup> The coupled product 5 was converted to ketone 6 in two steps (70% overall yield). Its regio- and stereoselective enolization using lithium hexamethyldisilazide<sup>9)</sup> followed by sulfonylation with phenyltriflimide<sup>10)</sup> afforded Z-enol triflate 7<sup>11)</sup> selectively (70%). Displacement of the triflate with a methyl group by lithium dimethylcuprate<sup>8)</sup> (20 mol eq., -15°C, 17h), however, did not proceed and the starting material was recovered. Higher order cuprate [Li<sub>2</sub>Cu(CN)-Me<sub>2</sub>]<sup>12)</sup>, prepared from 10 mol eq. of CuCN and 20 mol eq. of methyl lithium, resulted in a formation



(a) n-BuLi, -78°C, THF. (b) (i) CrO<sub>3</sub>·2py; (ii) Al(Hg), 65°C, THF-H<sub>2</sub>O. (c) LiN(TMS)<sub>2</sub>, PhNTf<sub>2</sub>, THF, -78°C. (d) MeLi (30 eq), CuCN (20 eq), THF, -4°C, 38 h.

of only trace amount of the desired olefin 1a together with alkyne 8 (63%) and the ketone 6 (6%). Finally, a successful methylation was achieved by using a cuprate with less MeLi [CuCN (20 mol eq.) and MeLi (30 mol eq.)] to afford a 4:1 mixture of 1a<sup>11)</sup> and 8 in 50% yield (based on recovered starting material) in 33% conversion (THF, -4°C, 38h).<sup>13)</sup> The recovered 7 could be recycled.

Thus, the condensation of 2 and 4 followed by the construction of C14-C15 double bond of 1a was performed. The reduced reactivity of 7 can be attributed to the presence of several oxygen substituents in the molecule. Improvement of the yield by using other protecting groups, particularly on C13 hydroxyl, as well as the coupling with the southern subunit<sup>4)</sup> are in progress.

#### References and Notes

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- 6) Prepared from dimethyl (S)-malate via the following sequence: (a) LDA, MeI (60%); (b) LiAlH<sub>4</sub>; (c) acetone, H<sup>+</sup>; (d) BnBr, NaH (42%, 3 steps); (e) 1H HCl, EtOH; (f) TBSCl, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (g) MEMCl, i-Pr<sub>2</sub>NEt (76%, 3 steps); (h) AcOH, H<sub>2</sub>O (3 : 1), 40°C; (i) PCC (85%, 2 steps, 4); (j) MeLi; (k) PCC (44% yield, 2 steps, 3). A similar route was adopted by Hanessian; see, reference 2.
- 7) The unreactivity can be attributed to the presence of oxygen substituents in 3, which can coordinate with the metal cation, since the coupling with a sterically demanding ketone such as 3-methy-2-butanone proceeded smoothly; however, the geometric selectivity of the Julia-Kocienski procedure<sup>5)</sup> in the trisubstituted olefin synthesis was unsatisfactory (E/Z = 2 : 1).
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- 13) 7 was readily separated by silica gel flash chromatography from the mixture of 1a and 8, which were separable by HPLC with Varian Si-5 column (50 cm x 8 mm) and hexane-ether (5 : 1) as eluent.