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# AVERMECTIN ANALOGS WITH A SPACER BETWEEN THE AGLYCONE AND THE DISACCHARIDE

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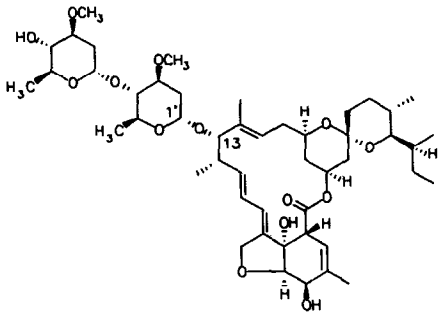
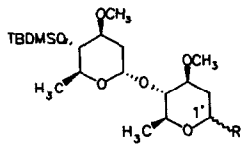
**Abstract:** Ivermectin (**1**) has been converted to several analogs in which a spacer unit has been inserted between the aglycone and the disaccharide. Analogs **9** and **10** retain good bioactivity while analogs **15**, **16**, **21**, and **22** are substantially less active than **1**.

The avermectins are a family of naturally occurring macrocyclic lactones with important anthelmintic and pesticidal activity.[1] Ivermectin (**1**),[2a] a semi-synthetic avermectin analog, is widely used as an anthelmintic agent in human and animal health.[1c,d] The economic importance of the avermectins has generated considerable interest in their chemical modification[2] as well as total synthesis.[3] The avermectins consist of an aglycone linked to a disaccharide and for some time we have been interested in modifying the connection between these substructures. We felt that altering the relative spatial orientation of the aglycone and the disaccharide or changing the strength of the link between them might have an interesting effect on biological activity. When we initially began work in the avermectin field such modifications were impractical. However, recent research on avermectin synthesis has resulted in the availability of the avermectin disaccharide (**2**)[2b,3b] and activated disaccharides (**3**)[3a,4a] and (**4**).[3b,4d] Access to these intermediates, coupled with recent advances in avermectin glycosylation,[3a,b] enabled us to successfully complete the conversion of **1** to several analogs (**9**, **10**, **15**, **16**, **21**, and **22**) in which various spacer units have been inserted between the aglycone and the disaccharide.

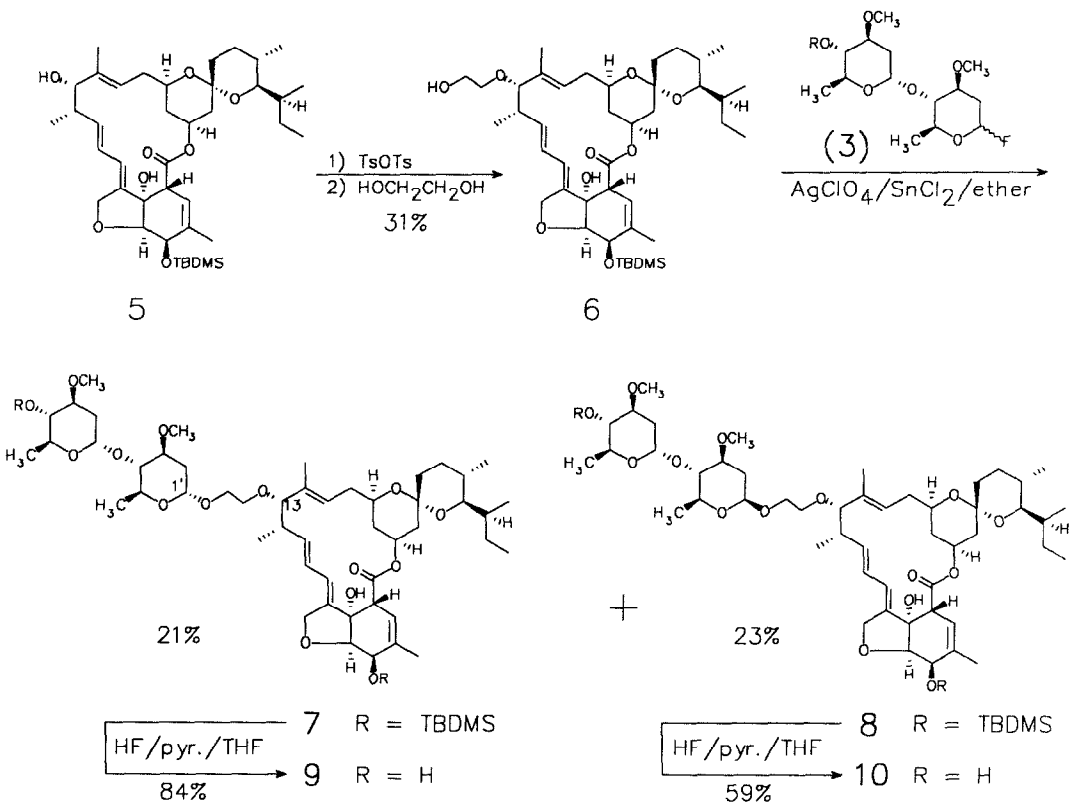


IVERMECTIN (1)

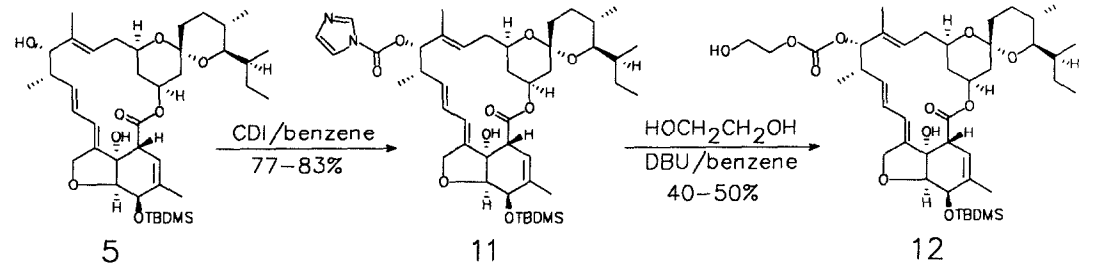


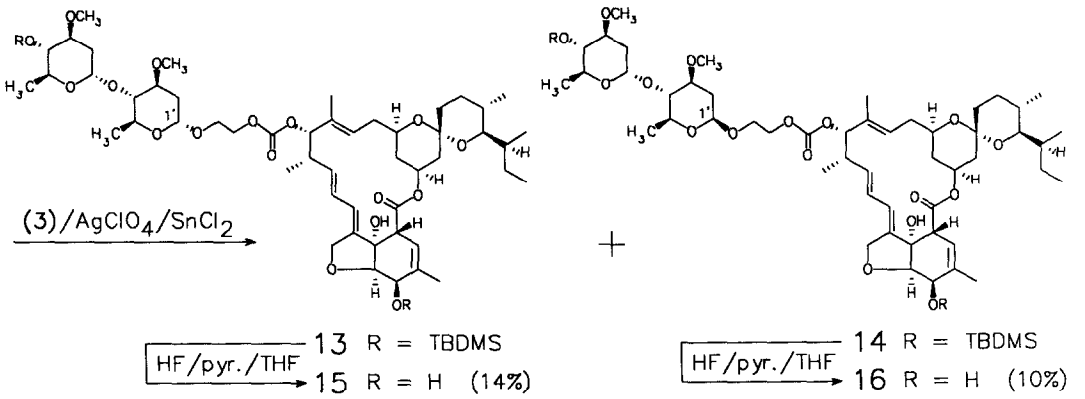
2 R = H
3 R = F
4 R = S-(2-pyridyl)

We chose analog **9** as our first target since the spacer is relatively small and is attached to the aglycone by a relatively stable ether linkage. We anticipated that the requisite intermediate **6** could be obtained via a procedure analogous to one previously used to prepare the 13-O-methyl analog.[2c] As expected, conversion of protected aglycone **5**[2c,d] to the tosylate[5a] (3.8 eq. $Ts_2O$,[5b] 6.2 eq. $(^iPr)_2NEt$, 5.9 eq. DMAP,[5c] $CHCl_3$, 23 °C, 18 h) followed by reaction of the crude tosylate with ethylene glycol ($HOCH_2CH_2OH$, 12.5 eq. KOAc, 55 °C, 6.5 h) afforded hydroxyethyl analog **6**[6a,b] (31% yield from **5**). Glycosylation of **6** with disaccharide-fluoride **3**[4a] (2.8 eq. **3**, 1.2 eq. $AgClO_4$, 1.3 eq. $SnCl_2$, ether, 3A sieves, *stirred vigorously*, 0 °C, 1 h)[3a] afforded both the α-glycoside **7** (21%) and the β-glycoside **8** (23%) (separated by preparative TLC on silica gel). Subsequent removal of the TBDMS[5d] protecting groups (HF/pyridine/THF) from **7** and **8** afforded the desired "spacermectin" analogs **9**[6b] (84%) and **10**[6b] (59%), respectively.

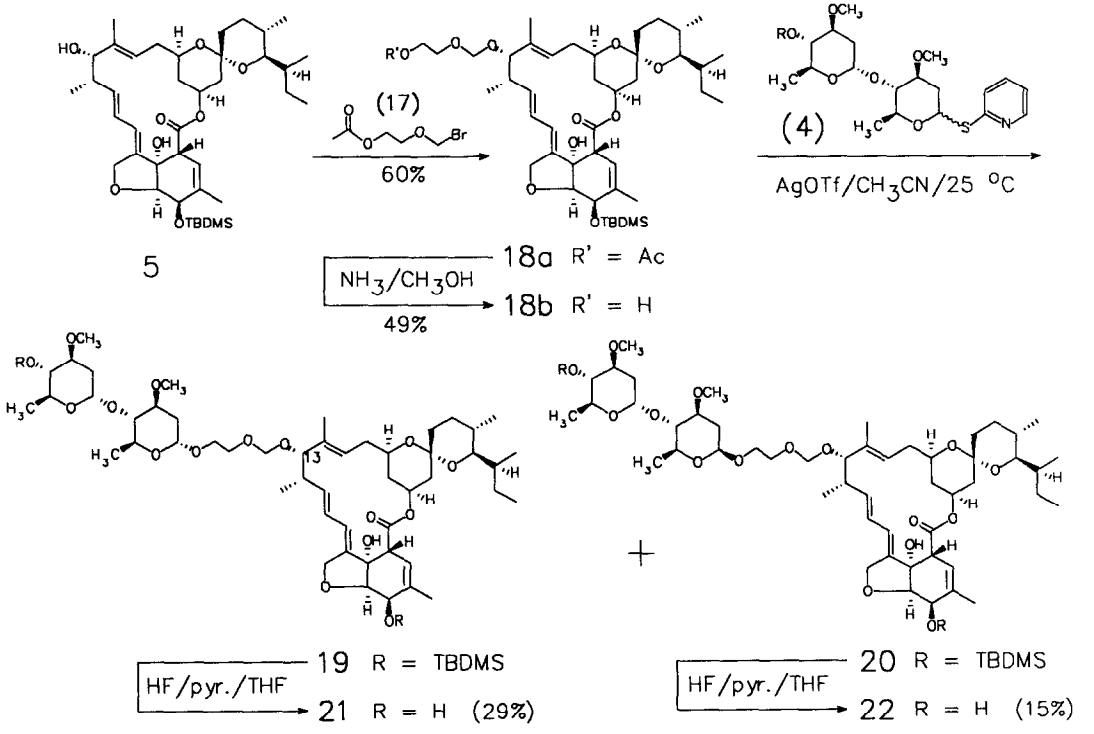



We next turned our attention to the preparation of analogs **15** and **16**. In these derivatives the spacer is slightly longer than in **9** and the connection to the aglycone should be more easily broken than the ether linkage in **9**. Reaction of **5** with CDI[5e] in benzene (1.2 eq. CDI, benzene, 23 °C, 28 h) afforded the stable intermediate **11**[6b] (77-83% chromatographed yield). Treatment of **11** with ethylene glycol in benzene (3.7 eq. $HOCH_2CH_2OH$, 0.2 eq. DBU,[5f] benzene, 23 °C, 21 h) provided the hydroxyethyl-carbonate **12** (40-50%). As expected, glycosylation of **12** (2.4 eq. **3**,[4a] 1.25 eq. $AgClO_4$, 1.2 eq. $SnCl_2$, ether, 3A sieves, *stirred vigorously*, 0 °C, 1.5 h)[3a] afforded both the α-glycoside **13** and the β-glycoside **14** which were deprotected (HF/pyridine/THF) to afford the desired "spacermectin" analogs **15** (14% from **12**) and **16** (10% from **12**).






Finally, we selected analogs **21** and **22** as targets based on the expectation that they would be intermediate in stability relative to the previous analogs. Condensation of **5** with 2-acetoxyethoxymethyl bromide (**17**)[7] (5 eq. **17**, 13 eq. $(^{i}Pr)_2NEt$, $CH_2Cl_2$, reflux, 31 h) afforded acetoxyethoxymethyl analog **18a** (60%). Treatment of **18a** with ammonia-saturated methanol (23 °C, 5 h) then provided the requisite hydroxyethoxymethyl intermediate **18b** (49%). Since the previous glycosylations using disaccharide-fluoride **3** had resulted in relatively low yields we decided to examine an alternative glycosylation method for the synthesis of **21** and **22**. Thus, reaction of **18b** with the thiopyridyl-disaccharide **4**[3b,4d] (1.5 eq. **4**, 1.3 eq. AgOTf,[5g] $CH_3CN$, 25 °C, 10 min.) afforded a 60:40 mixture of the α- and β- glycosides **19** and **20** (59%). The mixture was deprotected (HF/pyridine/THF) to afford the desired analogs **21** (29%) and **22** (15%) (separated by preparative reverse phase HPLC).



The novel analogs were evaluated in a brine shrimp immobilization assay (Table I).[8] Although analogs **9** and **10** were nearly as active as ivermectin, the other analogs were substantially less active. It appears that the activity of the analogs correlates directly with the stablity of the aglycone-disaccharide linkage. It is also interesting to note that with the possible exception of the carbonate analogs **15** and **16**, the glycoside stereochemistry ($\alpha$ or $\beta$) does not appear to have a significant effect on activity.

TABLE I

Bioactivity of Avermectin Analogs

| Compound | *A. Salina*[a] $IC_{100}$(ng/mL) |
|---|---|
| **1** | 430[b] |
| **9** | 1730 |
| **10** | 1730 |
| **15** | >55500[c] |
| **16** | 41650 |
| **21** | 27800 |
| **22** | 27800 |

(a) Brine shrimp (*A. salina*) data obtained as described in reference 8, average of 2 assays unless otherwise noted; (b) average of 3 assays; (c) Highest level tested, <100% activity.

## References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4. (a) Disaccharide-fluoride **3**[3a] was prepared by treating **2**[2b] with DAST[4b,c,5h] in $CH_2Cl_2$ (1.25 eq. DAST, -20 °C --> 23°C, 15 min.) followed by evaporation of $CH_2Cl_2$ and dissolution in ether (used immediately without purification); (b) Rosenbrook, W.; Riley, D.A.; Lartey, P.A. Tetrahedron Letters 1985, 26, 3; (c) Posner, G.H.; Haines, S.R. Tetrahedron Letters 1985, 26, 5; (d) Thiopyridyl-disaccharide **4**[3b] is stable and can be stored in a freezer for several months. It was prepared by reaction of **2** with 2,2'-dipyridyl disulfide (Aldrithiol™-2, Aldrich)[4e] and tributylphosphine (1 eq. Aldrithiol™-2, 1 eq. $Bu_3P$, $CH_2Cl_2$, 23 °C, 23 h) followed by flash chromatography (65-80% chromatographed yield); (e) Stewart, A.O.; Williams, R.M. J. Am. Chem. Soc. 1985, 107, 4289.
5. (a) tosylate = p-toluenesulfonate; (b) $Ts_2O$ = p-toluenesulfonic anhydride (Aldrich); (c) DMAP = 4-dimethylaminopyridine; (d) TBDMS = *tert*-butyldimethylsilyl; (e) CDI = 1,1'-carbonyldiimidazole (Aldrich); (f) DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene (Aldrich); (g) AgOTf = silver trifluoromethanesulfonate (Aldrich); (h) DAST = diethylaminosulfur trifluoride (Aldrich).
6. (a) Yields are unoptimized; all new compounds were characterized by $^1H$ NMR and FAB-MS; (b) satisfactory elemental (C,H) analysis was obtained for this compound.
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