141. Building Blocks for the Synthesis of Maytansinoids

Preliminary Communication

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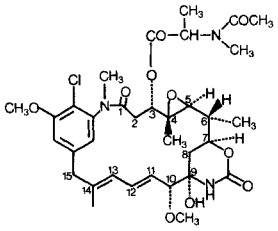
Summary

The dienal **14** and the ketone **19**, both potential building blocks of maytansinoids, were synthesized starting from ethyl vanillate (**2**) *via* the aldehyde **9**. It could be shown in a preliminary experiment that the dienal **14** can be coupled with 2-lithio-1,3-dithiane to afford compound **16** which exhibits the correctly substituted aromatic part of maytansine as well as its C(9) to C(15) moiety.

In our studies toward the synthesis of maytansinoids [1], *e.g.* maytansine (**1**), we have developed some time ago the preparation of the dienal **14** which we consider a useful intermediate for the synthesis of this interesting group of *ansa*-macrolides [2]. The recent announcement of the successful achievement of the same type of intermediate [3] as well as the publication of various routes to the 'aromatic part' of maytansine [3–5][1]) prompt us to disclose our synthesis of **14** and of the ketone **19**, another possible intermediate in this series.



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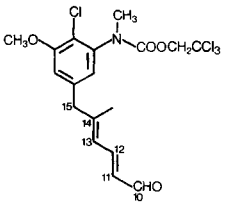

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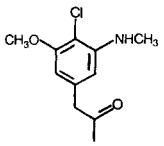
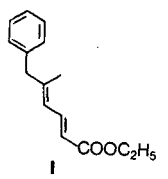


19

Ethyl vanillate (**2**) was nitrated by a mixture of nitric and acetic acids to give the nitro compound **3**, m.p. 121–122° (75%). Conversion of **3** to the chloro derivative **4**, m.p. 93–95° (73%), was performed by treatment with phosphoryl chloride in DMF in presence of equimolar amounts of lithium chloride and *s*-collidine. Reduction of **4** to the aniline derivative **5**, m.p. 120–122°, was achieved either with zinc in acetic acid (87%) or by catalytic hydrogenation (Pd/C) in HCl-ethanol (82%). **5** was converted into the *N*-methyl-derivative **8** by two different routes. Formylation of **5** with ethyl or phenyl formate (15 h at 80°) furnished **6**, m.p. 142–145° (84–94%), which was reduced by lithium aluminium hydride in THF. The resulting alcohol **8** was isolated as its hydrochloride, m.p. 195–196° (83%, based on **6**). Alternatively, reductive methyla-

[1]) For other papers in this synthetic area see [7] [8].

tion of **5** with formaldehyde in methanol in presence of hydrogen and *Raney*-nickel gave the ester **7**, m.p. 73–75° (65%), and subsequent reduction with REDAL also yielded **8** (51% as hydrochloride, based on **7**). Oxidation of the amino alcohol **8** with *Cornforth* reagent afforded the benzaldehyde derivative **9**, m.p. 58–59° (72%).



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The further pathway from **9** to the dienal **14** – with **13** → **14** as critical step – was designed with the knowlege that the model ester I[2]) did not show any deconjugation on refluxing with sodium ethoxide in ethanol. Therefore, one could anticipate that a diene system such as in structure **12** would be easely shifted to a position as in **14** on unmasking the terminal aldehyde group.

9 was condensed with propionaldehyde (potassium hydroxide, ethanol) to **10**, m.p. 98–100° (70%). Elogation of the side chain was realized by reaction of **10** with an excess of the *Grignard* reagent prepared from 2-(2'-bromoethyl)-dioxolane [6] yielding the alcohol **11**[3]), m.p. 110–111° (94%). Dehydration of **11** in refluxing toluene catalysed by *p*-toluenesulfonic acid afforded the diene **12**[3]) (55% after chromatography; 41% after recrystallisation: m.p. 79–81°). The hydrolysis of the acetal function necessitated prior acylation of the amino group, otherwise cyclisation to a dihydronaphthalene took place. Reaction of **12** with 2,2,2-trichloroethoxycarbonyl chloride in pyridine, followed by hydrolysis of the crude carbamate **13** with 1 N aqueous hydrochloric acid/acetone at 50° furnished a 2:1 mixture of the two stereo-isomeric dienals **14** and **15** (60–70%), the main component (**14**) of which could be isolated by chromatography (silica gel, ethyl acetate/hexane). Under the conditions used for the hydrolysis of **13**, pure **14** was equilibrated to a 2:1 mixture of **14** and **15**.

According to ^{1}H-NMR.-spectroscopy ($CDBr_3$, 270 MHz), at room temperature both isomers **14** and **15** each exist in two rotameric forms. At 80° the duplicity of the relevant signals has disappeared. The pure *E,E*-compound **14** at room temperature shows the following NMR.-signals (270 MHz, $CDCl_3$): 1.88 (*s*, CH_3–C(14)); 3.26 (*s*, CH_3–N); 3.46 (*s*, H_2C(15)); 3.90 (*s*, CH_3–O); 4.46, 4.91 (2*d*[4]), O–CH_2–CCl_3, J=12 Hz); 6.13 (*d*×*d*, H–C(11), $J_{11,12}$=15 Hz, $J_{10,11}$=8 Hz); 6.20 (*d*, H–C(13), $J_{12,13}$=11 Hz); 6.70 (*d*, arom.H, J=2 Hz); 6.76 (*d*, arom.H, J=2 Hz); 7.39 (*d*×*d*, H–C(12), $J_{11,12}$=15 Hz, $J_{12,13}$=11 Hz); 9.60 (*d*, H–C(10), $J_{10,11}$=8 Hz); [the minor rotamer exhibits distinct extra signals at 1.91 (*s*, CH_3–C(14)); 3.32 (*s*, CH_3–N)]. The *E,E*-configuration of **14** was confirmed by ^{13}C-NMR.

The carbonyl carbon in **14** corresponds to C(10) of maytansine and, for the future elaboration to the target molecule, must be connected to C(9) of an appropriate 'aliphatic' building block. In order to demonstrate the usefulness of **14** for this purpose, the C(9)–C(10) coupling was simulated in a preliminary experiment: Reaction of the 2:1 mixture of **14** and **15** with 2-lithio-1,3-dithiane in THF at −70°, followed by *in situ* methylation with methyl iodide in THF/HMPT [7] and, finally, treatment of the crude product with zinc in methanol/acetic acid provided a 2:1 mixture of the two isomeric methoxy compounds **16** and **17** (totally 40%, based on

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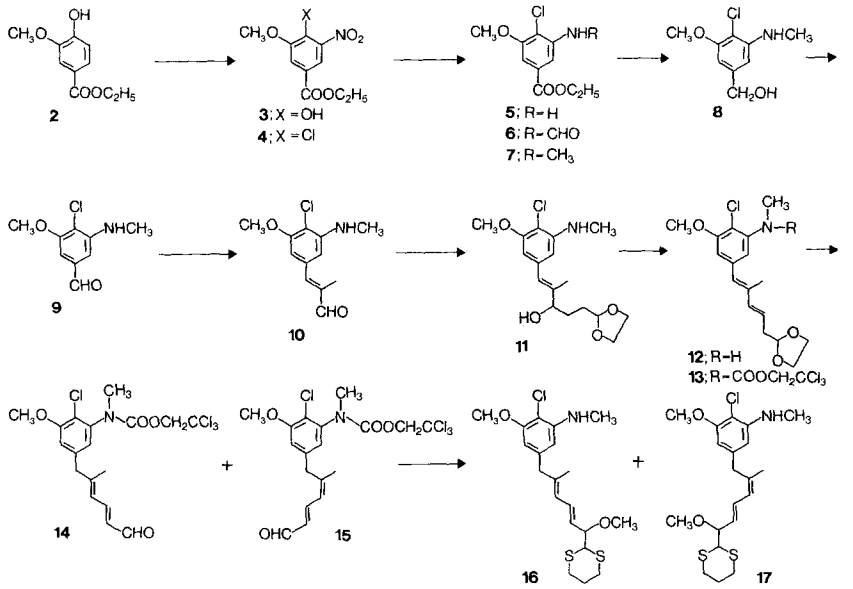
[2]) Obtained from benzyl methyl ketone by a *Horner* type condensation as *E,E*/*E,Z*-mixture.

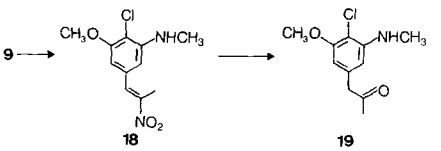
[3]) One single isomer; configuration of the benzylidene double bond unknown.

[4]) The unequivalence of the two methylene protons must be due to a second hindrance of rotation.



14+**15**). The *E,E*-configuration of the major component **16** was proven by NOE with the mixture.

Finally, we would like to mention the preparation of the ketone **19** as another possible intermediate in this synthetic field: Condensation of **9** with nitroethane in presence of ammonium acetate (15 min reflux) afforded **18**[3]), m.p. 84–85° (86%) which by reduction and hydrolysis (ethanol/hydrochloric acid, iron powder, ferric chloride, 80°) yielded **19** (86%; liquid, purified by chromatography).



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