Tetrahedron Letters, Vol. 34, No. 27, pp. 4397-4398, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Borane Complexes of Vinblastine Type Diindole Derivatives

Mihály Balázs,[a] Csaba Szántay Jr.,[b,c] Hedvig Bölcskei[b] and Csaba Szántay[a*]

[a] Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1025 Budapest, POB 17, Hungary.

[b] Chemical Works of Gedeon Richter Ltd., ([c]Spectroscopic Research Centre), H-1475, Budapest, POB 27, Hungary.

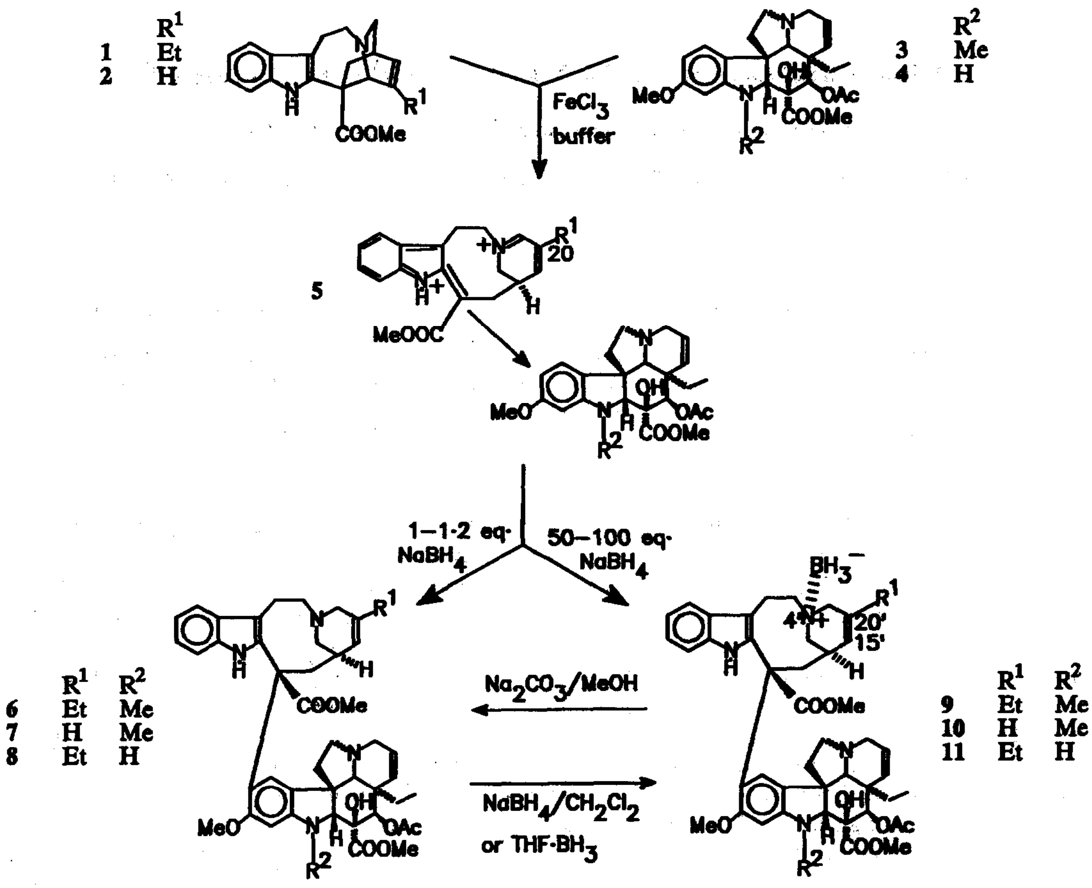
Key Words: Anhydrovinblastine; 20'-deethyl-AVLB; N-demethyl-AVLB; borane complexes; $FeCl_3$ coupling.

Abstract: *While investigating the ferric chloride mediated coupling[1] of catharanthine* (**1**) *with vindoline* (**3**) *and their derivatives* (**2**,**4**), *the borane complexes of 15',20'-anhydrovinblastine[2] (AVLB), 20'-deethyl-AVLB and N-demethyl-AVLB* (**9**,**10**,**11**) *have been synthesized. The corresponding bases* (**6**,**7** *and* **8**) *have also been obtained in high yield.*

Vincristine - vinblastine type diindole alkaloids are well known for their anticancer activity.[3] Besides the naturally occurring compounds (isolated from *Catharantus Roseus*), synthetic derivatives are also used in cancer chemotherapy (e.g. Navelbine®).[4] Earlier we reported on the methodical investigation of the ferric chloride coupling method, in which catharanthine (**1**) was coupled to vindoline (**3**) to give anhydro-vinblastine (AVLB) (**6**) in over 70% isolated yield.[2] Unfortunately AVLB is usually contaminated by significant amounts of oxidative side-products (most notably leurosine), which encumbers the transformation of AVLB into navelbine. Slightly modified conditions of the coupling reaction led us to a new derivative, the borane complex of AVLB (**9**), in 80% yield. The latter proved to be highly stable against oxidative influences, and could easily be transformed into the desired base (**6**). The borane complexation of the basic nitrogen of the catharanthine part presumably prevents, sterically and electronically, the tetrahydropyridine ring from oxidative side-reactions.

We have employed the ferric chloride coupling method to other catharanthine and vindoline derivatives. Sundberg and Langlois coupled 20-deethylcatharanthine (**2**) with vindoline (**3**) via the Polonovski-Potier reaction in 16% yield.[5] In aqueous medium in the presence of ferric chloride we obtained 20'-deethyl-AVLB (**7**) in 28% yield. A modification of the reductive work-up led us to the 20'-deethyl-AVLB borane complex (**10**) (mp 200°C, decomp.). When coupling catharanthine (**1**) to N-demethylvindoline (**4**), the Polonovski-Potier method resulted in N-demethyl-AVLB (**8**) in 40% yield.[6] By using the ferric chloride procedure we isolated **8** in more than 70% yield. When applying an extreme excess of sodium borohydride, a new derivative, the N-demethyl-AVLB borane complex (**11**) was obtained (mp 208-210°C, decomp.). Similarly to our earlier results reported for the AVLB borane complex (**9**),[2] detailed spectroscopic studies verified that the complexation site involves N'-4, with the BH_3 group being in α position in the new borane complexes **11** and **10**.[7] Refluxation of the complexes **10** and **11** in methanol in the presence of sodium carbonate[8] allowed the easy production of the corresponding bases, **7** and **8**, respectively. The bases **6**, **7** and **8** can be transformed into their borane complexes directly by sodium borohydride in dichloromethane or in tetrahydrofurane-borane.

Assuming the formation of the dication **5** as proposed by Vukovic et al.[1], **5** can attack the aromatic ring of vindoline and subsequently stabilize as the dimeric compound. When **1** is involved in the coupling reaction, the electron donating effect of the 20-ethyl group facilitates the formation of **5**, giving similar yields for **6** and **8**. However, in the case of 20-deethylcatharanthine (**2**) the beneficial influence of the ethyl group is absent, and formation of the dication is less favoured which results in a dramatic decrease in the yield of 20'-deethyl-AVLB (7). These observations conform to the depicted mechanism.



REFERENCES AND NOTES

1. Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron*, **1988**, *44*, 325-331.
2. Szántay, Cs., Jr.; Balázs, M.; Bölcskei, H.; Szántay, Cs. *Tetrahedron*, **1991**, *47*, 1265-1274.
3. Zavala, F.; Guenard, D.; Potier, P. *Experientia* **1978**, *34*, 1497-1499.
4. EP 10.458 patent (Pierre Fabre).
5. a) Gueritte, F.; Langlois, N.; Langlois, Y.; Sundberg, N.J.; Bloom, I.D. *J. Org. Chem.* **1981**, *46*, 5393-5395. b) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.*, **1976**, *98*, 7017-7024.
6. Gedeon Richter Ltd. Belg. 867.255. (Cl.CO7D), Hung. Appl. 632, CA **90** 138 081 S.
7. Details and other physical data are available upon request.
8. a) Picot, A.; Lusinchi, X. *Bull. Soc. Chim. Fr.*, **1977**, 1227-1234. b) Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.*, **1973**, *95*, 612-613.

(Received in UK 18 May 1993)