Novel Amidoalkylation of 4-Acetoxyazetidinones with Allylic Boranes. A Stereoselective Entry into the Tribactams

Tino Rossi,* Stefano Biondi,* Stefania Contini, Russell J. Thomas, and Carla Marchioro

Glaxo Research Laboratories via Fleming 4, 37135 Verona, Italy

Received June 8, 1995

Tricyclic β-lactams **1** (tribactams), first synthesized in our laboratories, are members of a new class of β-lactam antibacterial agents associated with an extremely good biological profile[1] (Figure 1). A member of this class, sodium (4*S*,8*S*,9*R*,10*S*)-4-methoxy-10-[(*R*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (**2**) (GV104326), has shown particularly good activity against a wide range of bacteria[2] (including β-lactamase-producing strains) and is currently in phase II clinical studies. Due to their particular structure, bearing five stereogenic centers, there was a need for an efficient stereoselective synthesis of this class of compounds. Here we report a stereoselective synthesis of 4-cyclohexenylazetidinone **4** through a novel reaction[3] between commercially available 4-acetoxyazetidinone[4] **3** and suitable *B*-cyclohex-2-enyldialkylboranes **5** (Scheme 1). Compound **4** can be considered a key intermediate in the synthesis of GV104326 (**2**) and, in general, of (8*S*) (or 8β) 4-substituted tribactams **1**.

Although the existing route[1c] to 4-cyclohexenylazetidinone **4** has been used for the production of multikilogram quantities of **4**, it suffers from two major drawbacks: (a) low overall chemical yield (40%) and (b) relatively high number of reactions required (three steps, five chemical transformations). Preliminary studies have also already demonstrated that a one-step synthesis of intermediate **4**, through an intramolecular Sakurai-type reaction, is possible,[5] but stereoselectivity and chemical yield were not considered satisfactory for large-scale use.

Despite the fact that 4-acetoxyazetidinone **3** has been found to react with several allylating agents such as allylcuprates,[6] allylzinc halides,[7] and allylsilanes and allylstannanes,[8] there is no precedent in the literature for reactions between **3** and allylboranes. Moreover, the well-known *B*-cyclohex-2-enyldialkyl boranes (**5**) have been reported to react with aldehydes with high *syn* selectivity.[9a,b] For these reasons we became very interested in studying the reactivity of allylboranes with **3**.

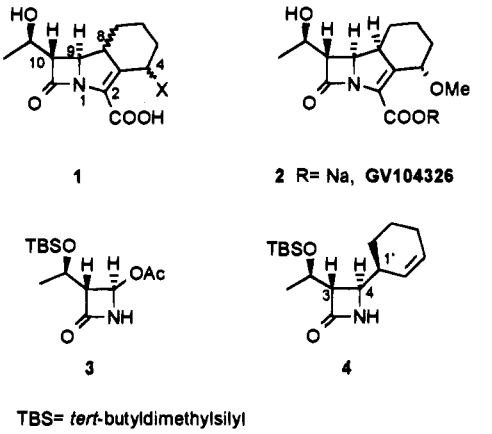


Figure 1.

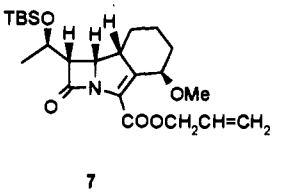
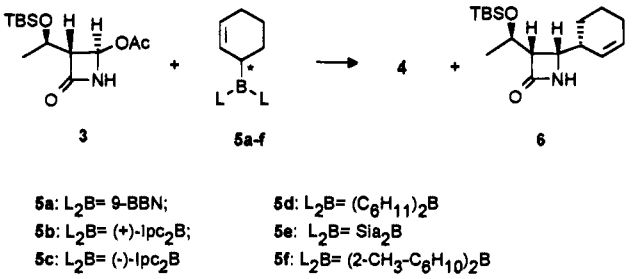


Figure 2.

Scheme 1



5a: L_2B= 9-BBN; **5d**: L_2B= $(C_6H_{11})_2B$
5b: L_2B= (+)-Ipc_2B; **5e**: L_2B= Sia_2B
5c: L_2B= (-)-Ipc_2B **5f**: L_2B= $(2\text{-}CH_3\text{-}C_6H_{10})_2B$

When *B*-cyclohex-2-enyl-9-borabicyclo[3.3.1]nonane (**5a**) was reacted with acetoxyazetidinone **3** at room temperature (mixture hexane/THF as solvents, see Scheme 1), the desired compound **4** was isolated after workup and flash chromatography in 30% yield as a single isomer. To our surprise, an equal amount of a second reaction product **6** was isolated from the reaction mixture. The stereochemistry of compound **6** was confirmed by its conversion to fully protected tribactam **7** (Figure 2), according to a well-established protocol.[1c] Further proof of the structure of **6** was obtained by X-ray crystallography.[10]

We found that the addition of a mild Lewis acid (Et_3Al) effectively accelerated the reaction and increased the isolated yield (see Table 1). Further studies led us to establish that a number of Lewis acids increase the reaction rate,[11] diethylzinc giving the best results of those screened.[12] These results were obtained with racemic **5a**. To assess the role of the asymmetric center on the cyclohexenyl ring of **5a** in determining the

(1) (a) Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso, R.; Bismara, C. Eur. Pat. Appl. EP0416953 A2, 1991; *Chem. Abstr.* **1992**, *116*, 235337t. (b) Perboni, A.; Rossi, T.; Gaviraghi, G.; Ursini, A.; Tarzia, G. WO 9203437, 1992; *Chem. Abstr.* **1992**, *117*, 7735m. (c) Perboni, A.; Tamburini, B.; Rossi, T.; Donati, D.; Tarzia, G.; Gaviraghi, G. In *Recent Advances in the Chemistry of Anti-Infective Agents*; Bentley, P. H., Ponsford, R., Eds.; RSC: Cambridge, 1992; pp 21−35.

(2) Di Modugno, E.; Erbetti, I.; Ferrari, L.; Galassi, G. L.; Hammond, S. M.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362.

(3) Biondi, S.; Rossi, T.; Contini, S. A. EP 617017, 1994; *Chem. Abstr.* **1994**, *121*, 280531r.

(4) (3*R*,4*R*,1′*R*)-(+)-4-Acetoxy-3-[1′-(*tert*-butyldimethylsilyl)oxy]ethyl]−2−azetidinone (**3**) is commercially available, from Aldrich Chemical Company Inc., Milwaukee, WI.

(5) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1995**, *36*, 4283.

(6) Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098.

(7) Imuta, M.; Itani, H.; Ona, H.; Hamada, Y.; Uyeo, S.; Yoshida, T. *Chem. Pharm. Bull.* **1991**, *39*, 663.

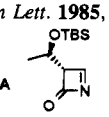
(8) For a recent review on the role of organotin and organosilicon compounds in the synthesis of β-lactams, see: Veinberg, G. A.; Lukevics, E. *Heterocycles* **1994**, *38*, 2309.

(9) (a) Brown, H. C.; Bhat, K. S. *J. Org. Chem.* **1986**, *51*, 445. (b) Brown, H. C.; Bhat, K. S.; Jadhav, P. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2633 and references cited therein.

(10) The structure of compound **6** has been also confirmed by X-ray crystallography of its 3-hydroxyethyl derivative obtained by fluoride ion mediated deprotection of compound **6**. Details will be reported in a full paper.

(11) Similar yields (but longer reaction times) were observed without addition of Lewis acids when 3 equiv of **5a** was used.

(12) It is believed that the mild Lewis acids accelerated the reaction rate by favoring the formation of the azetinone reacting species **A**; see: Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1985**, *26*, 6309.



0002-7863/95/1517-9604$09.00/0

Table 1

entry	borane (equiv)[a]	L.a. (equiv)[b]	temp, °C	time, h	yield (**4** + **6**),[c] %	ratio **4**:**6**[d]
1	**5a** (3)		23	24	87	57:43
2	**5a** (2.2)	Et_3Al (1)	23	6	>95	41:59
3	**5a** (2.2)	$Al(O\text{-}i\text{-}Pr)_3$ (1)	23	8	85	51:49
4	**5a** (2.2)	$Ti(O\text{-}i\text{-}Pr)_4$ (1)	23	3	95	52:48
5	**5a** (2.2)	Et_2Zn (1)	23	1.5	95	49:51

[a] Referred to the equivalents of BBN used in the hydroboration of cyclohexadiene. [b] L.a. = Lewis acid. [c] Isolated yield after flash chromatography. [d] Determined by NMR measurements on the crude reaction mixture.

Scheme 2

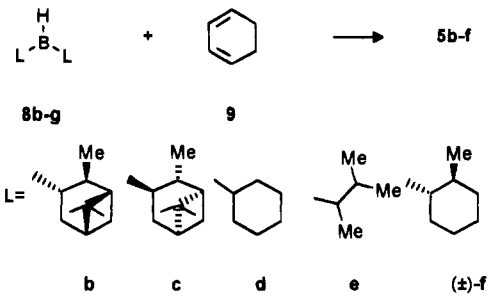


Table 2

entry	borane (equiv)[a]	L.a. (equiv)	temp, °C	time, h	yield (**4** + **6**),[b] %	ratio **4**:**6**[c]
1	**5b** (3)	Et_2Zn (1)	0	6	95	95:5
2	**5c** (3)	Et_2Zn (1)	0–23	8	85	25:75
3	**5b** + **5c** (3)	Et_2Zn (1)	0	8	90	70:30
4	**5d** (4)	Et_2Zn (1)	0	6	95	52:48
5	**5e** (4)	Et_2Zn (1)	0	6	91	68:32
6	**5f** (4)	Et_2Zn (1)	0–23	6	96	95:5

[a] Referred to the equivalents of BH_3·DMS used in the hydroborations. [b] Isolated yields after flash chromatography. [c] Ratios determined by NMR on the crude reaction mixture except for entries 1–3, where terpene-containing fractions were removed by filtration on a silica pad before analysis by NMR.

stereoselectivity of the process, we repeated the reaction with *B*-(cyclohex-2-enyl)diisopinocampheylborane **5b** (from (−)-α-pinene, see Scheme 2) and were pleased to obtain **4** with both high yield and high stereoselectivity. It has been shown for **5b** and its enantiomer that the allylic isomerization could invert the absolute configuration at C-1 of the cyclohexenyl ring, resulting in a loss of selectivity in the subsequent reaction. As, at temperatures below −10 °C, the reaction was not found to proceed to any appreciable extent, the reaction temperature was selected as a compromise between reactivity and selectivity. We found that at 0 °C we obtained almost quantitative yields together with good diastereoselectivity.

In order to ascertain if the observed stereoselectivity was due to a double diastereoselection effect, we repeated the reaction with the enantiomer **5c** (Table 2, entry 2). The reaction was much slower and required higher temperatures, giving an incomplete reversal of selectivity. We believe this result to be due to a "mismatched" double diastereoselectivity. This theory was supported by the experiment with a racemic mixture of boranes **5b** and **5c** (Table 2, entry 3); under these conditions, a 7:3 mixture of **4** and **6** was obtained, highlighting the preferential formation of "matched" **4**.

Despite the fact that with racemic **5a** no stereoselectivity was obtained (Table 1, entry 5), the observation that azetidinone **3** was able to exert a "kinetic resolution" in the case of a racemic mixture of **5b** and **5c** prompted us to continue the study of racemic *B*-(cyclohex-2-enyl)dialkylboranes. We selected three alkyl ligands structurally related to Ipc, namely, cyclohexyl, siamyl, and α-methylcyclohexyl (Scheme 2, compounds **5d**–**f**). In the case of borane **5d** no stereoselectivity was observed (Table 2, entry 4), with borane **5e** an encouraging 2:1 selectivity in favor of isomer **4** was obtained (Table 2, entry 5), and finally, the use of an excess of racemic borane **5f** gave **4** in both high yield and high selectivity (Table 2, entry 6).[13]

The reasons for the unexpectedly high diastereoselectivity observed are still not completely understood and will require further studies. At present it seems that a methyl group α to the carbon bearing the boron atom on the ligand could be responsible for the stereocontrol,[14] possibly by modifying the preferred conformations in the transition state,[15] resulting in a difference in energy between the transition state generated by the isomer with an (*R*) configuration at the carbon of the cyclohexenyl moiety bearing the boron atom and its epimer.

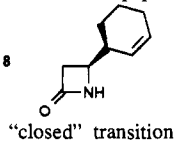
We have thus demonstrated that alkenyldialkylboranes **5a**–**f** can react with 4-acetoxyazetidinone **3** to give cyclohexenylation products **4** and **6**. By selection of the appropriate reagent (**5b** or **5f**), a one-pot synthesis of 4-cyclohexenylazetidinone **4** in up to 90% yield and synthetically useful diastereoselectivity was established. This compound has been found to be a key intermediate not only in the synthesis of GV104326 **2** but also for other 4-substituted tribactams that have been synthesized in our laboratories.[16]

Supporting Information Available: Characterization data for compounds **4**, **6**, and **7** and proofs of stereochemistry of **2** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

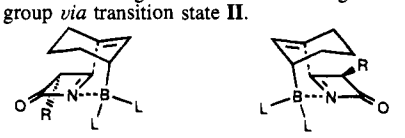
JA951857C

(13) The use of borane **5f** gave results comparable with those obtained with **5b** and allowed us to eliminate the use of pinene, whose availability in bulk quantities could cause potential problems during scale-up studies.

(14) A referee had suggested that the siloxyethyl side chain may be involved in stereocontrol. However, preliminary studies show that the 3-unsubstituted analog of **3** reacts with **5b** to give compound **8** with 88% ee. The details will be reported in a full paper.



(15) For this reaction a "closed" transition state is proposed: *syn*-selectivity at C-4 and C-1′ has been explained through a favored "chair-like" transition state; compound **4** originates from the borane having an (*R*) absolute configuration at the stereogenic center of the cyclohexenyl moiety through transition state **I** whereas isomer **6** originates from the isomer with an (*S*) absolute configuration at the stereogenic center of the cyclohexenyl group *via* transition state **II**.



(16) All of the compounds synthesized were characterized by routine analytical and spectroscopic methods.