Synthesis of the Paralytic Shellfish Poisons (+)-Gonyautoxin 2, (+)Gonyautoxin 3, and (+)-11,11-Dihydroxysaxitoxin

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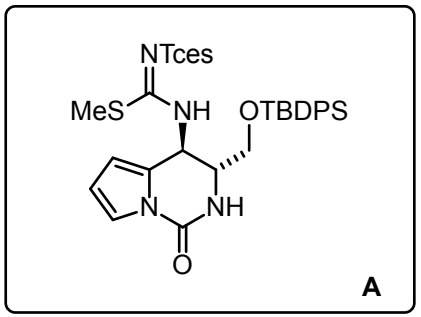
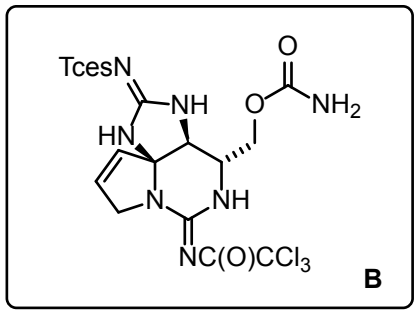
L-serine methyl ester hydrochloride

1 – 5



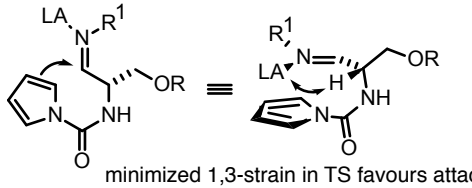
A

6 – 12



B

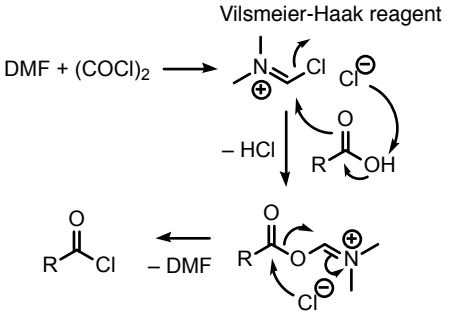
1) pyrrole-1-carboxylic acid, $(COCl)_2$, cat. DMF, aq. $NaHCO_3$, THF
2) TBDPSCl, imidazole, DMF
3) *i*-BuAlH, DCM, –90 °C
4) allylamine *then* $BF_3 \cdot OEt_2$, DCM
5) $Pd(PPh_3)_4$, 1,3-dimethylbarbituic acid, DCM *then* TcesNC(SMe)Cl, aq. Na_2CO_3



minimized 1,3-strain in TS favours attack from *re*-face

6) EtOTf, 2,4,6-tri-*t*-butylpyrimidine, DCM
7) NH_3, NH_4OAc, MeOH, 70 °C
8) $Cl_3CC(O)Cl$, *i*-Pr_2NEt, DCM
9) $Rh_2(esp)_2$ (cat.), $PhI(OAc)_2$, MgO, DCM, 40 °C
10) $BF_3 \cdot OEt_2$, Et_3SiH
11) n-Bu_4NF, THF
12) $Cl_3CC(O)CNCO$, *then* MeOH

Please give a mechanism for step 1



Please give name and mechanism for step 4 and explain why one diastereomer is preferred (dr: >20:1)

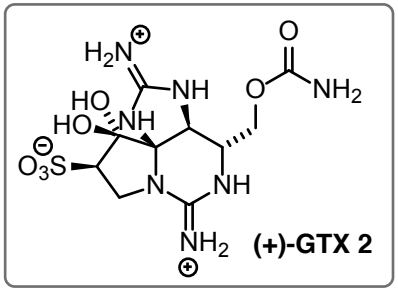
Pictet-Spengler reaction

Step 6: can you imagine why this transformation proved to be challenging?

Answer see page 3

Please suggest a mechanism for step 9

Answer see page 3



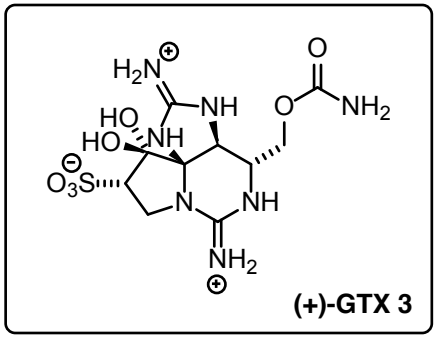
(+)-GTX 2

13 – 18

13) OsO_4 (cat.), NMO, THF
14) PhC(O)CN, DMAP, –78 °C
15) DMP, DCM
16) H_2, Pd/C, MeOH, CF_3COOH
17) NH_3, MeOH
18) DMF · SO_3, 2,6-di-*t*-butyl-4-methylpyridine

Step 18: what is the role of the pyridine?

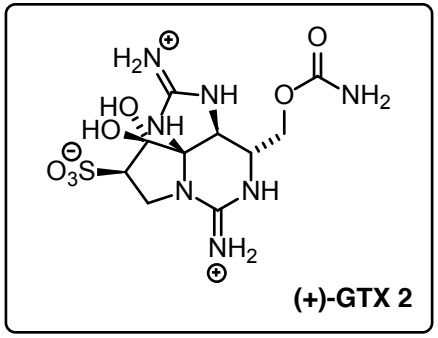
Sterically hindered base to buffer reaction mixture



(+)-GTX 3

19

19) 0.3 M aq. NaOAc



(+)-GTX 2

Bonus question: The gonyautoxins as well as closely related saxitoxins are highly potent toxins. Can you imagine how they work?

GTX and STX bind in the extracellular pore of Na_V and sterically block ion permeation by binding the reentrant loops that form the Na^+ selectivity filter.

Step 6: can you imagine why this transformation proved to be challenging?

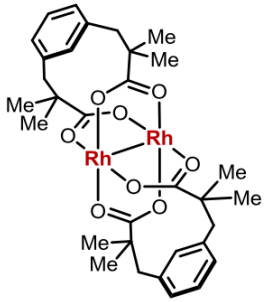
The authors assume that the **pyrrole group stronly reduces the nucleophilicity of the urea oxygen towards alkylation** which is why the method used by *Kishi et al.* (tetraethyl oxonium tetrafluorobirate) was not successful. *Overman et al.* used $MeOSO_3CF_3$ in combination with a sterically hindered base (2,6-di-t-butyl-4-methylpyridine). However in the present publication these conditions gave **competetive N-methylation**.
The authors could achieve selective O-alkylation (1:1) by applying a more hindered electrophile EtOTf which gave an improved O:N alkylation ratio of 3:1,
further modifications (temperature and base) gave O:N-alkylation ratio of 9:1.

Mechanistic insight for step 9:

Nitrene Transfer Catalysis
mixed valent Rh(II,III) species; Rh_2(II,III)-nitrene complex, concerted C-H abstraction/ N-C and N-H bond formation very likely

$PhI(OAc)_2$ serves as oxidant, MgO as base to neutralize AcOH

methodology and mechanistic insight please see
Org. Lett. **2006**, *8*, 1073.
Tetrahedron **2009**, *65*, 3042.
J. Am. Chem. Soc. **2016**, *138*, 2327.



$Rh_2(esp)_2$