

Alternating Pyrazine Organic Semiconductor Polymers

by: Robert B. Login rloginconsulting.com

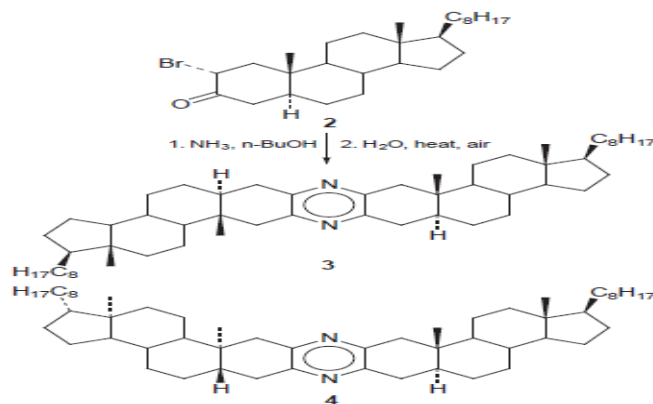
I previously proposed methods based on alpha-amino ketones to produce a variety of pyrazine polymers that would be of interest as semiconductor components. This past proposal can be found on my web page ([Alpha-Amino Ketone based Polymeric Pyrazines](#)

Alpha-amino ketones available from the Neber rearrangement and other reactions can be employed to prepare unique polypyrazines useful in semiconductor applications.)

Although I believe that dimerization of alpha-amino ketones to form pyrazines (after oxidation) is a well accepted reaction and a high yield method. I did not present much evidence for this and was not aware of the extensive cephalostatins and ritterazines pyrazine antineoplastics synthesis literature. For example:

“The symmetrical dimeric steroid-pyrazines can be obtained by the classical condensation of α -amino ketones that is, actually, the most efficient method of pyrazine ring construction.”

“The initially formed 2a-amino-3-ketones undergo spontaneous dimerisation to a mixture of dihydropyrazines, which are then oxidized by air.”

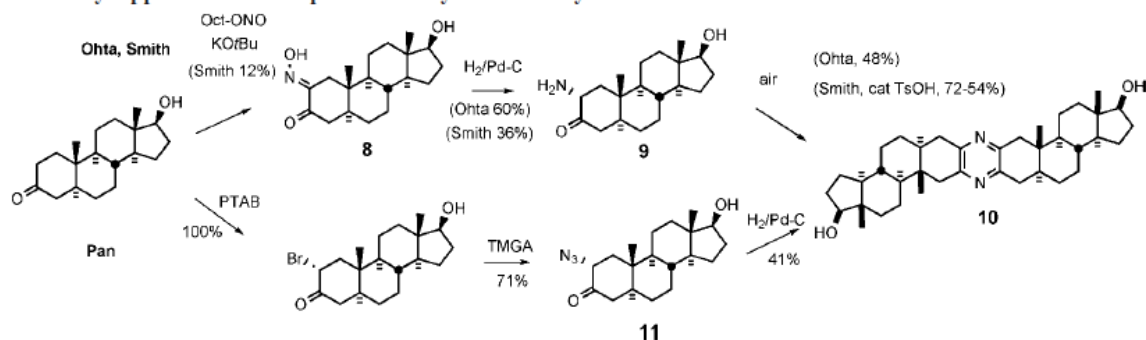


Scheme 1

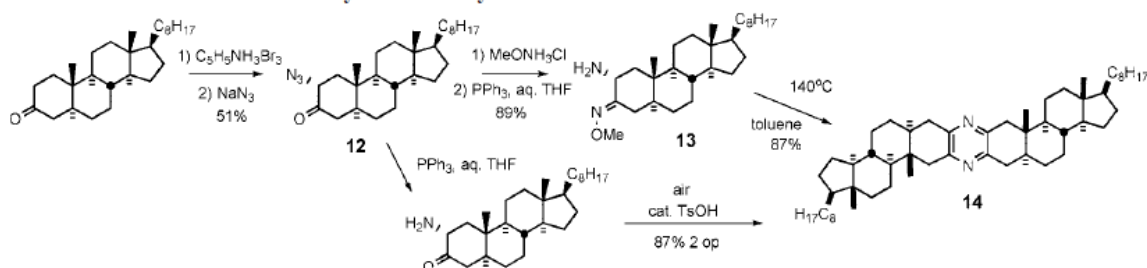
Łotowski, Z., Gryszkiewicz, A., Borowiecka, J. B., Nikitiuk, A., & Morzycki, J. W. (1999). A facile synthesis of symmetrical dimeric steroid-pyrazines. *Journal of Chemical Research, Synopses*, (11), 662-663.

Recently, more sophisticated synthesis procedures were developed because these dimeric steroid-pyrazines are some of if not the most active cancer cell killers that do not harm normal cells. The major problem is not the final step, the pyrazine synthesis, but the complexity of the steroid structures. It's amazing that these cancer cell killers are the product of lowly marine creatures!

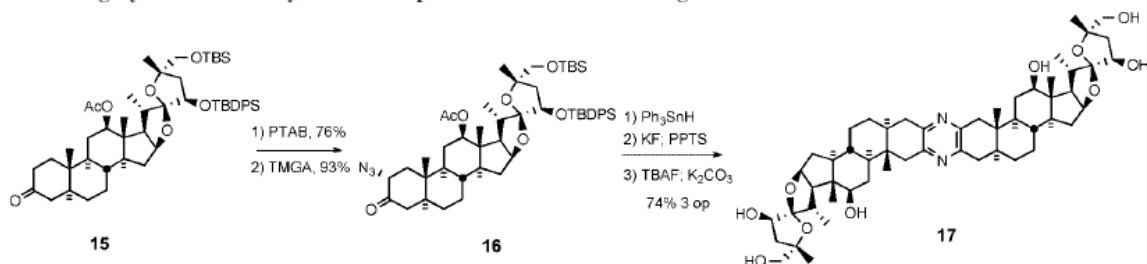
Scheme 4. Early Approaches for Preparation of Symmetrical Pyrazines



Scheme 5. Smith/Heathcock Routes to Symmetrical Pyrazines



Scheme 6. Jeong Synthesis of C₂-Symmetric Cephalostatin North 1 Analogue



Lee, S., LaCour, T. G., & Fuchs, P. L. (2009). Chemistry of trisdecacyclic pyrazine antineoplastics: The cephalostatins and ritterazines. *Chemical reviews*, 109(6), 2275-2314.

The rest of the above excellent review illustrates how to put together the pyrazine when the two sides (referred to as north and south) have different structures.

These pyrazine synthesis procedures can afford high yields, as much as 87%. These high yields are with the coupling of rather large compounds much as would be expected during my polypyrazine synthesis proposals. Therefore, I feel that my previous proposal for unique pyrazine polymers would indeed have a chance of working. At that time, I did not dwell on the synthesis of the starting alpha-amino ketones and looking at the above Chem. Rev., that would have benefited my ideas. This then leads to my latest polypyrazine proposal.

Coming across references dealing with haloalkynes, gave me another idea for pyrazine alternating polymers.

Terminal Alkynes:

Adding terminal alkynes to a vast variety of aromatics with the Sonohisigara and other reactions are well known procedures resulting in high yields, straight forward work-ups and reasonable costs.

Chinchilla, Rafael, and Carmen Nájera. "The Sonogashira reaction: a booming methodology in synthetic organic chemistry." *Chemical reviews*, 107.3 (2007): 874-922.

Chinchilla, Rafael, and Carmen Nájera. "The Sonogashira Reaction." *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*, (2014): 269-298.

Alonso, Diego A., et al. "Solid-Supported Palladium Catalysts in Sonogashira Reactions: Recent Developments." *Catalysts*, 8.5 (2018): 202.

Additional methods:

Müller, S., Liepold, B., Roth, G. J., & Bestmann, H. J. (1996). An improved one-pot procedure for the synthesis of alkynes from aldehydes. *Synlett*, 1996(06), 521-522.

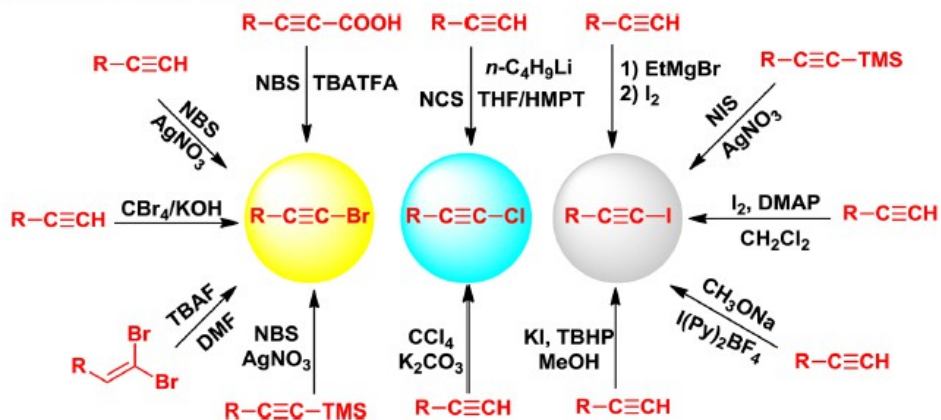
Pietruszka, Joerg, and Andreas Witt. "Synthesis of the Bestmann-Ohira reagent." *Synthesis*, 2006.24 (2006): 4266-4268.

Corey, E. J., and P. L. Fuchs. "A synthetic method for formyl→ ethynyl conversion ($RCHO \rightarrow RC \equiv CH$ or $RC \equiv CR$)." *Tetrahedron Letters*, 13.36 (1972): 3769-3772.

Haloalkyne synthesis:

Reactions of said terminal acetylenes to alpha-haloalkynes is straight forward.

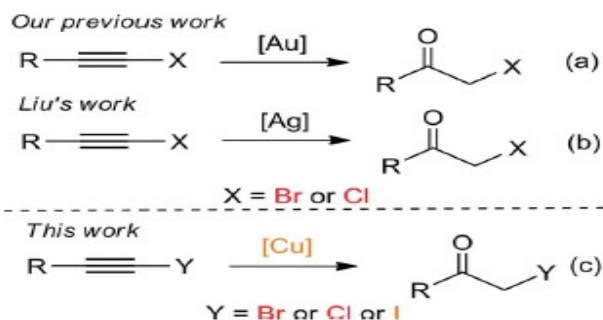
Scheme 2. Preparation Methods for Haloalkynes



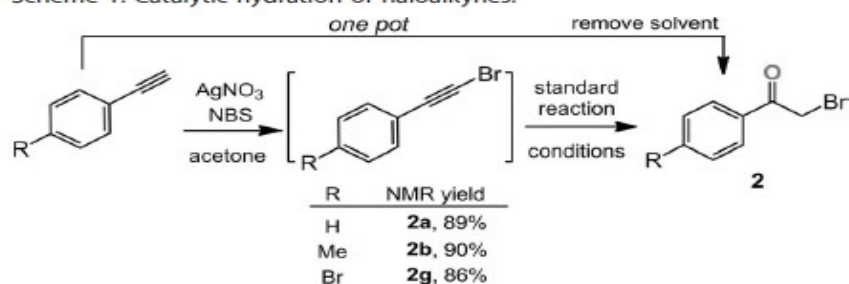
Wu, Wanqing, and Huanfeng Jiang. "Haloalkynes: a powerful and versatile building block in organic synthesis." *Accounts of chemical research*, 47.8 (2014): 2483-2504.

Alpha-haloketones:

Zou et. al. invented a method for the conversion of haloalkynes to alpha-haloketones with a safe recyclable catalyst system. This approach is less toxic and much more environmentally acceptable versus the previous methods based on noble metals, not to mention cheaper and scale-able.



Scheme 1. Catalytic hydration of haloalkynes.



Scheme 3. One-pot protocol: sequential process.

Zou, H., He, W., Dong, Q., Wang, R., Yi, N., Jiang, J., ... & He, W. (2016). First Catalyzed Hydration of Haloalkynes by a Recyclable Catalytic System. *European Journal of Organic Chemistry*, 2016(1), 116-121. And references cited therein.

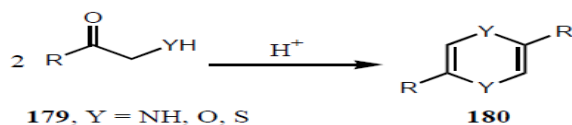
Now I'm not saying that haloalkynes are the only or the best method of synthesizing alpha-haloketones. The reason I like this approach is because semiconductor intermediates are readily derivatised with terminal alkynes. (Also semiconductor intermediates are readily derivatised with terminal aldehydes that can also be readily transformed into alkynes but the Sonohisigara alkyne approach looks simpler.)

Pyrazines:

Conversion of the alpha-haloketone to the corresponding alpha-amino ketone is also well known.

The dimerization of the phenacyl derivatives **179**, readily obtainable from α -haloketones and amines, NaOH or Lawesson's reagent, is one of the convenient synthetic route for the preparation of pyrazine [394-398], 1,4-dioxin [399-401] and 1,4-dithiin [402,403] derivatives **180** (Scheme 52).

Scheme 52

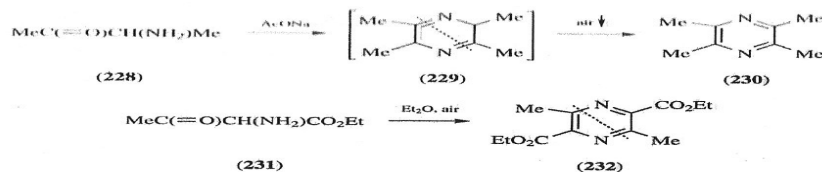


Erian, A. W., Sherif, S. M., & Gaber, H. M. (2003). The chemistry of α -haloketones and their utility in heterocyclic synthesis. *Molecules*, 8(11), 793-865.

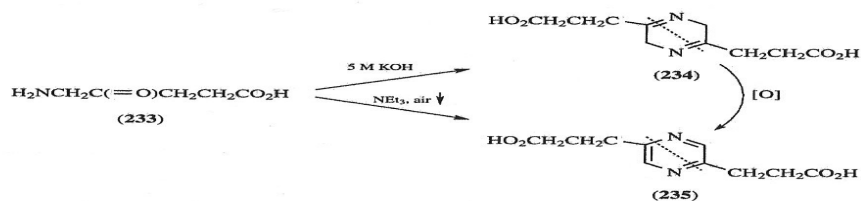
Using α -Aminoalkanones

3-Amino-2-butanone (**228**) gave 2,3,5,6-tetramethylpyrazine (**230**) via the unisolated dihydropyrazine (**229**) (AcONa, MeOH, air \downarrow , 60°C, 1 h: 73%); homologues likewise.⁹⁰¹

Ethyl 2-acetyl-2-aminoacetate hydrochloride (**231**) gave diethyl 3,6-dimethyl-2,5-pyrazinedicarboxylate (**232**) (Et₃N, EtOH, air, 20°C, 6 h: 90%).³⁹

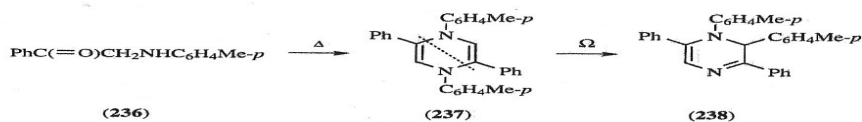


5-Aminolevulinic acid hydrobromide (**233**) gave 2,5-bis(2-carboxyethyl)pyrazine (**235**) (Et₃N, 3-Å molecularsieve, air \downarrow , 20°C, 3 days: 50%);⁵⁴² the intermediate 3,6-dihydro derivative (**234**) could be isolated as its HgCl₂ complex.²⁴⁴



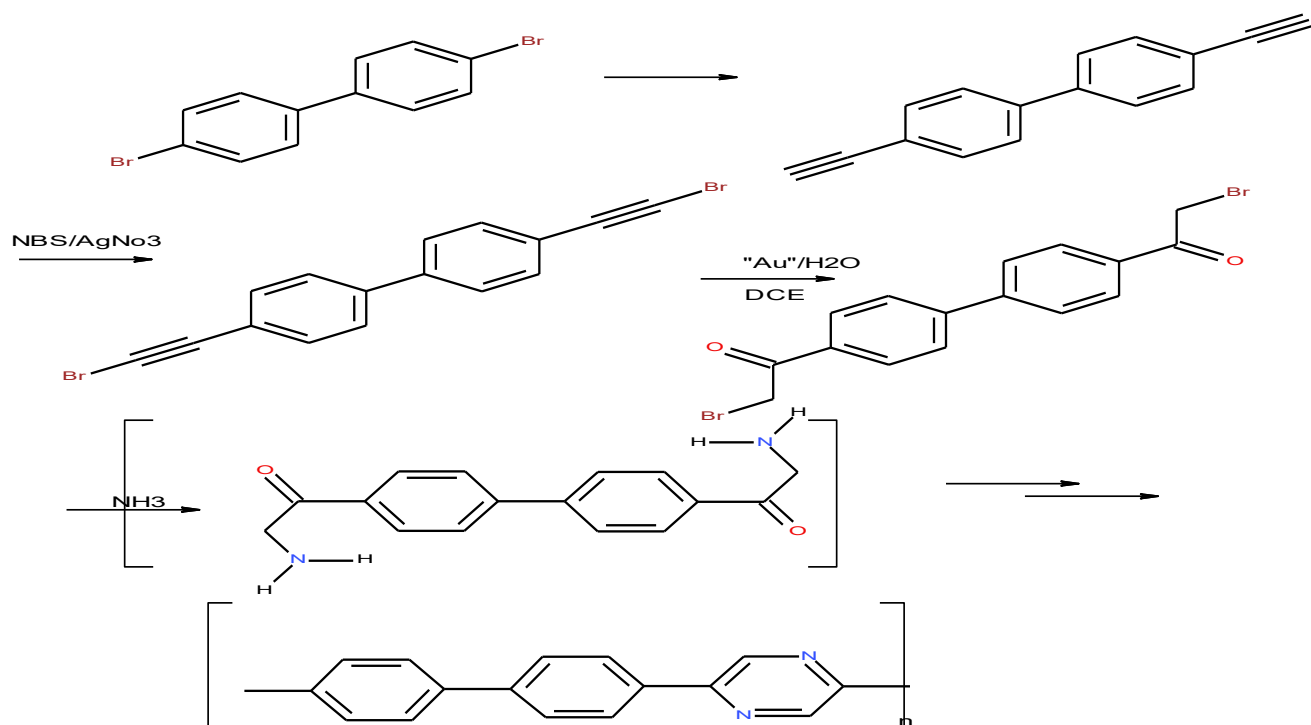
N-Phenacyl-*p*-toluidine (**236**) has been reported to give 2,5-diphenyl-1,6-di-*p*-tolyl-1,2-dihydropyrazine (**238**) (neat, N₂, 140°C, 16 h: 18%), probably by rearrangement of the isolable intermediate, 2,5-diphenyl-1,4-di-*p*-tolyl-1,4-dihydropyrazine (**237**).³¹

Also other examples.^{23, 26, 399, 580, 870, 1275, 1441, 1586}

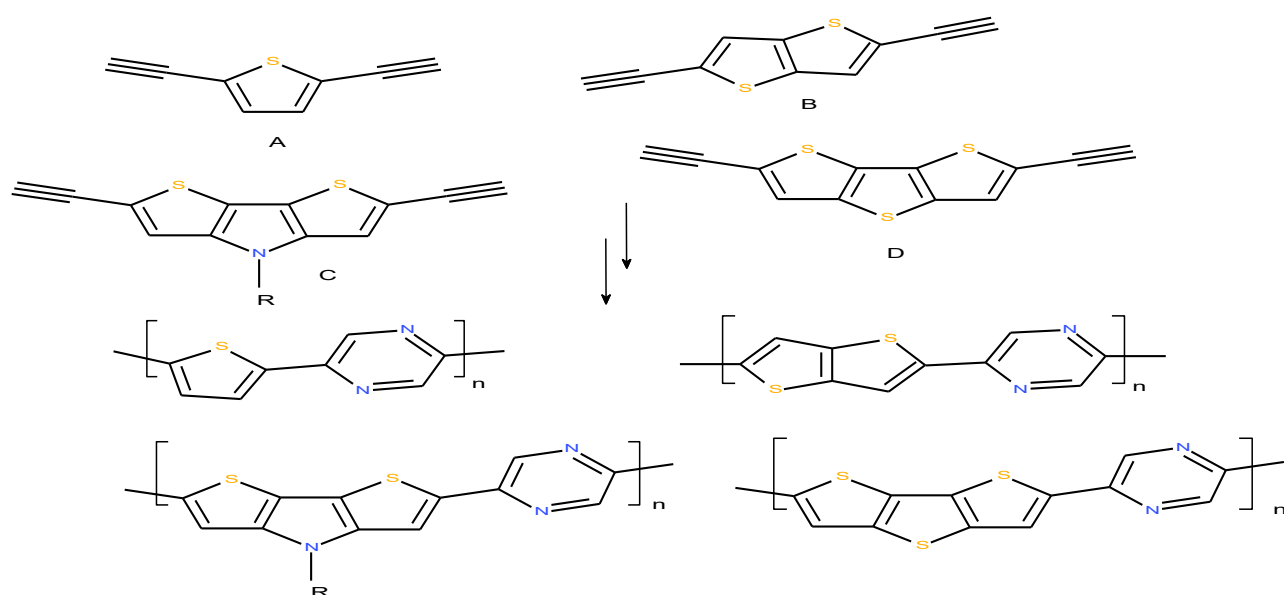


The Pyrazines (Supplement 1) by D. J. Brown, Wiley, 2002.

Like most organic chemical reactions, they are not all high yield. Actual experimentation is required but these references convince me that the reaction works and conditions required for high yields can be found.

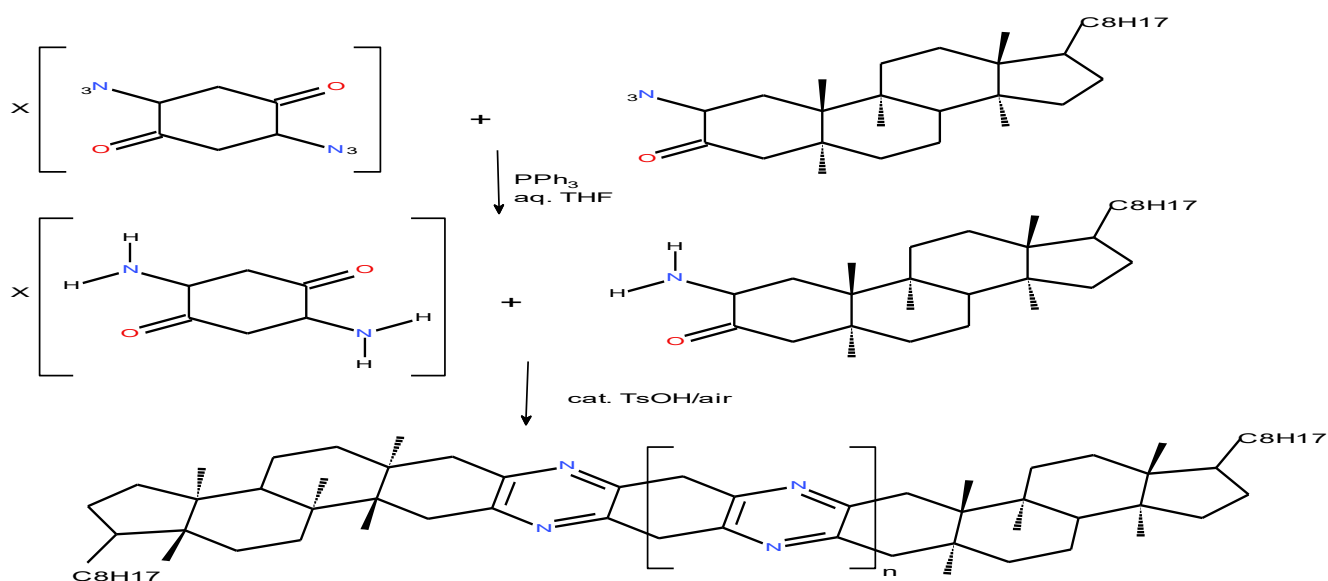


Scheme 1: An example of a possible semiconductor polymer. Silver and gold catalysts are not out of consideration, because they would produce purifiable small compounds and are not involved in polymer synthesis step.



Scheme 2: Examples of possible Donor-Acceptor semiconductor polymers.

Now combining the above with the cephalostatins and ritterazines pyrazine synthesis suggests experimental routes to new derivatives.



Scheme 2: Smith/Heathcock type pyrazine synthesis. With the trisdecacyclic steroidal alpha-amino ketone as a capping monomer, n can be greater than one.

If you want to actually prepare cephalostatins and ritterazine polypyrazine derivatives, then it's much more complicated because both sides (north and south) of the pyrazines are not identical and the final polypyrazine step is therefore more complicated, and if interested, there are numerous references to their synthesis starting with the above mentioned Chem Review.

Kumar, R. N., & Lee, S. (2017). Synthesis and bioactivity of bis-steroidal pyrazine 23-deoxy-25-epi ritterostatin GN1N. *Steroids*, 126, 74-78.

Fortner, K. C., Kato, D., Tanaka, Y., & Shair, M. D. (2009). Enantioselective synthesis of (+)-cephalostatin 1. *Journal of the American Chemical Society*, 132(1), 275-280.

Ambrose, A. J., Santos, E. A., Jimenez, P. C., Rocha, D. D., Wilke, D. V., Beuzer, P., ... & Costa-Lotufo, L. V. (2017). Ritterostatin GN1N, a Cephalostatin–Ritterazine Bis-steroidal Pyrazine Hybrid, Selectively Targets GRP78. *ChemBioChem*, 18(6), 506-510.

Thank you for reading these proposals. I would welcome suggestions, corrections, references etc.

Dr. Robert B. Login rloginconsulting.com