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ASSEMBLY OF THE GEPHYROTOXIN RING SYSTEM VIA A [4+1] APPROACH TO 3-PYRROLINES

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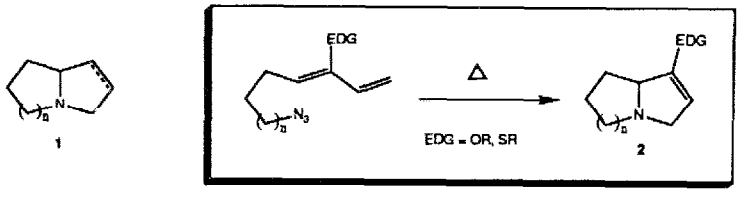
Abstract: Heating azidodienes **19** at 70°C produced the tricyclic 3-pyrrolines **20** and **21** in one operation. The diastereoselectivity of this process was examined, and found to be controlled by the conformation of the cyclization precursor. Compound **20d** incorporates the basic features of gephyrotoxin **3**.

Fused bicyclic pyrrolidines and 3-pyrrolines such as **1** are commonly found as structural features of naturally occurring compounds. We have recently reported a direct method for the assembly of such ring systems based on the intramolecular cyclization of azides with electron-rich 1,3-dienes (eq. 1).[1,2] The presence of an electron-donating group (EDG) at the position shown is crucial for the proper outcome of this cycloaddition/rearrangement,[3] and provides a useful functional group for the further elaboration of the resultant 3-pyrroline **2**. We wish to report the application of this method to the assembly of the tricyclic skeleton of the muscarinic antagonist gephyrotoxin **3**.[4] The key feature is the one step conversion of the azidodiene **19d** into **20d**.

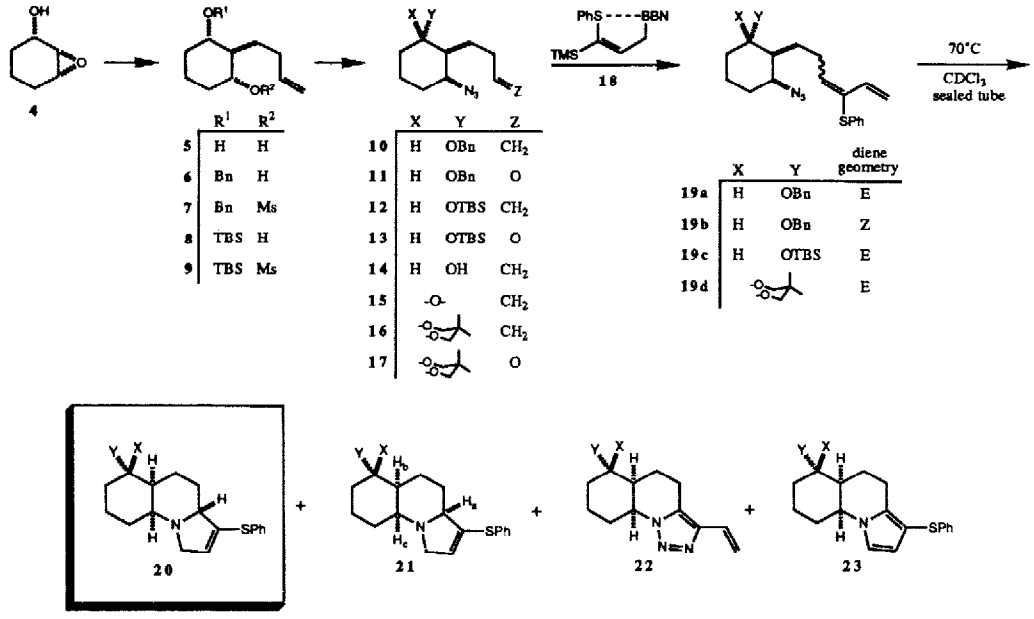
A crucial aspect of the planned approach to **3** was the diastereoselectivity of the initial intramolecular 1,3-dipolar cycloaddition of an azide with the proximal double bond of a tethered diene (see **19**). Preliminary examination of models led to ambiguous predictions, since both boat- and chair-like conformations of the forming six-membered ring provided reasonable alignment of the dipole and dipolarophile.[5] We hoped to explore this question with a model study.



1 2 (eq. 1)

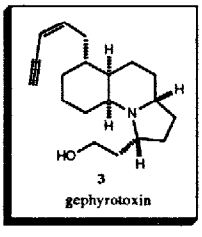
Regioselective ring opening of the epoxy alcohol **4**[6] with 3-butenylmagnesium bromide gave the 1,3-diol **5**.[7,8] Selective monobenzylation[9] provided **6**, which was converted into the azidoaldehyde **11** by standard methods. One pot conversion of **11** to either azidodiene *E*-**19a** or *Z*-**19b** was efficiently accomplished using our recently developed methodology.[10] Thus, hydroboration of 1-phenylthio-1-trimethylsilyl-1,2-propadiene with 9-BBN (35°, THF, 2h) and addition of the resultant allylborane **18** to **11** followed by workup with sodium hydroxide produced **19a** in near quantitative yield, exclusively as the *E* isomer. Alternatively, workup with sulfuric acid produced the *Z* isomer **19b** in good yield and excellent stereoselectivity.

Heating azidodienes **19a** and **19b** at 70° for 7d in deuteriochloroform in a sealed tube produced the cycloadducts **20** and **21** with low diastereoselectivity.[11] These two examples show that there is a slight



Series	Total Yield (%)	Ratio of 20 : 21 : 22 : 23**	Conditions
a	86	5 : 5 : 3.5 : 1	0.16M, 7d
b	--*	5 : 9 : 1 : 1.5	0.16M, 7d
c	--*	5 : 9 : 4 : 1	0.16M, 7d
d	90	13 : -- : 22 : 1	0.16M, 40h
d	90	10 : -- : 3 : 1	0.03M, 1eq. NH_4Cl, 70h
d	75	25 : -- : 4 : 1	0.16M, 1eq. NH_4Cl, 70h

*NMR experiment, isolated yields not determined
**Determined by NMR before purification

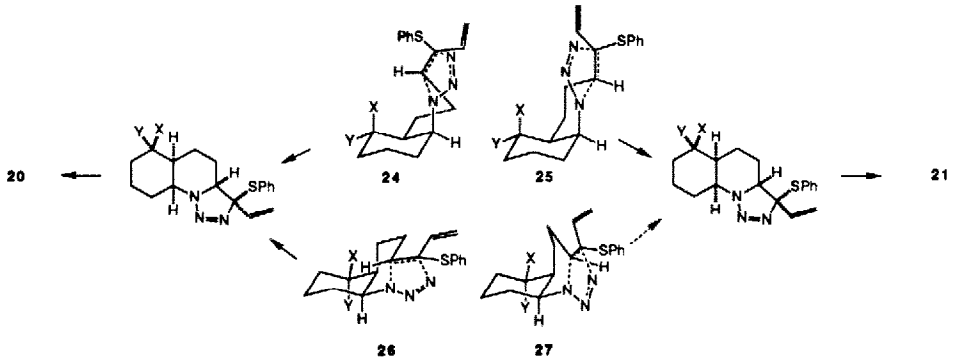


Transformations	Reagents	Yields (%)[8]
4 to 5	2.5 eq. CH_2=$CHCH_2CH_2MgBr$, 10% CuI, THF, -78° to RT, 2h	54*
5 to 6	NaH, THF; $PhCH_2Br$, 5% Bu_4NI, RT, 7h	99
6 to 7	CH_3SO_2Cl, NEt_3, CH_2Cl_2, -78° to 0°, 5h	99
7 to 10	5eq. nBu_4NN_3, THF, 35°, 24h	83
10 to 11	O_3, MeOH, -78°, 0.5h; Me_2S, -78°, 2h; 0°, 2h; RT, 6h	84
11 to 19a	18, THF, 0°; RT, 2h; 4N NaOH	99
11 to 19b	18, THF, 0°; RT, 2h; conc. H_2SO_4	70
5 to 8	NaH, THF, RT, 1h; $Me_2tBuSiCl$, 12h	99
8 to 9	CH_3SO_2Cl, NEt_3, CH_2Cl_2, -78° to 0°, 5h	96
9 to 12	5eq. nBu_4NN_3, THF, 35°, 24h	93
12 to 13	O_3, MeOH, -78°, 0.5h; Me_2S, -78°, 2h; 0°, 2h; RT 6h	91
13 to 19c	18, THF, RT; 4N NaOH	73
12 to 14	nBu_4NF, THF, RT, 5h	90
14 to 15	PCC, Celite, CH_2Cl_2, RT, 24h	--
15 to 16	$HOCH_2C(CH_3)_2CH_2OH$, cat. $(CO_2H)_2$, MeCN/hex, RT, 9h (ref. 14)	86**
16 to 17	O_3, MeOH, -78°, 0.5h; Me_2S, -78°, 2h; 0°, 2h; RT, 2h	99
17 to 19d	18, THF, RT, 18h; 4N NaOH, 4h	75

* plus 13% of 1,2-diol, easily separated by crystallization of 5.
** for two steps.

stereochemical dependence on the geometry of the diene. Changing the benzyloxy group of dienes **19a,b** to a bulky silyloxy group (see diene **19c**) had no appreciable effect on the stereochemical outcome of the reaction. Compound **19** (X=Y=H) was also prepared (not shown) to investigate the effect of a smaller substituent, but again, a ratio of approximately 1:1 was observed for **20** and **21**. In addition, variable amounts of triazoles **22** and pyrroles **23** were observed in the above cycloadditions. The former is a result of thiophenol loss from the intermediate vinyl triazoline, and the latter depends on how well the solution is deoxygenated. A convenient solution to these problems is presented below.

The low stereoselectivity of these reactions, and their relative independence from the size of the substituents at position Y in **19** are consistent with this group being equatorially situated in the preexisting six-membered ring, such as in **24** and **25**. We hoped to shift the diastereoselectivity in the desired direction by changing X into a larger group. This should favor transition state **26**, since 1,3-diaxial interactions are avoided. All attempts to prepare **19** where X=H, Y=OCH_2Ph were unsuccessful. However, ketal **19d** proved to be a nice solution to the stereochemical problem. We noticed immediately that this compound had a different conformation than dienes **19a-c**. In the ^1H NMR spectrum, the methine hydrogen next to the azide in **19d** had $w_{1/2}$=20 Hz, consistent with a conformation such as depicted in **26/27**, where the methine hydrogen is axial. In contrast, **19a-c** all had $w_{1/2}$=10 Hz, consistent with and equatorial methine hydrogen as in **24/25**. Should the reaction proceed through the chair-chair transition state **26**



rather than the chair-boat transition state **27**, the desired tricyclic compound **20** would result. In the event, heating **19d** for 70h at 70°C in deuteriochloroform produced a 90% yield of cyclized materials, with **20d** present as only one detectable diastereomer, although triazole **22d** was now the major product (**20d**:**22d**:**23d**=13:22:1). The triazole problem was solved by running the cyclization in the presence of ammonium chloride. This weak acid presumably aided in the ring cleavage of the intermediate triazoline, minimizing the chance for thiophenol elimination to a triazole. *Heating **19d** with one equivalent of NH_4Cl in deuteriochloroform at 70 °C for 70h produced **20d** as a single stereoisomer.* Analysis of the ^1H NMR spectrum of the reaction mixture prior to purification showed a 10:3:1 mixture of **20d**, **22d** and **23d** when the reaction was run at 0.03M, and a 25:4:1 ratio when run at 0.16M. Column chromatography provided pure **20d** in 45-50% isolated yield,[12] accompanied by ca. 10-15% of triazole **22d** and ca. 5-10% of pyrrole **23d**. Purification causes some oxidation of **20d** to **23d**, accounting for the differing ratios of crude versus isolated products.

The one step assembly of the tricyclic nucleus of gephyrotoxin bodes well for extension to the natural material. We have previously shown that Raney nickel may be used to reduce 3-phenylthio-3-pyrrolines to pyrrolidines.[1] Incorporation of the required hydroxyethyl sidechain remains to be accomplished, but should be accessible using a more substituted diene. Removal of the ketal would then intercept one of Kishi's intermediates.[4c,d] Also of interest is

the possible use of using enzymatic methods to convert the meso diol **5** into optically pure intermediates for a synthesis of the natural stereoisomer of gephyrotoxin.[13]

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3. Related cyclizations without an electron-donating group at the indicated position produce other products as a result of the variable chemistry of intermediate 2-vinyl aziridines.[2c,e-h] Some of these products are useful for alkaloid synthesis via a different disconnection.[2g,h] Exceptions which directly provide the desired type of 3-pyrrolines in special cases are those of Schultz[2c] and Naruta.[2d] Activated 2-vinyl aziridines (available from certain azide-diene cyclizations) may be rearranged to 3-pyrrolines by the action of iodide ion. See Scheiner[2a] and Hudlicky, T.; Sinai-Zingde, G.; Seoane, G. *Synth. Commun.* **1987**, *17*, 1555.
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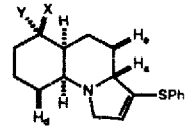
11. The stereochemistry of **21** (from dienes **19a-c**) was assigned by difference NOE and NOESY spectroscopy, where H_b and H_c showed an enhancement when H_a was irradiated. This enhancement was absent in **20**.
12. The stereochemistry of **20d** was assigned by difference NOE spectroscopy. After assignment of protons with COSY spectroscopy, irradiation at H_a caused enhancements at H_d and H_e:



20d

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