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A NEW STEREOSELECTIVE SYNTHESIS OF dl-PUMILIOTOXIN C USING NOVEL 1,3-BIS(TRIMETHYLSILYLOXY)-1,3-DIENES

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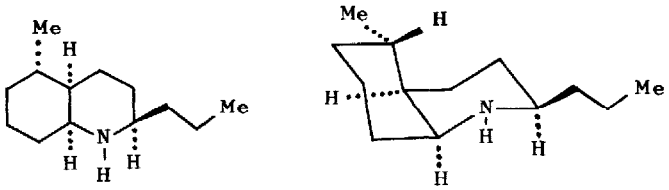
Pumiliotoxin C (1), originally isolated from Neotropical frogs Dendrobates pumilio and D. auratus,[1] has become of interest because of its nerve-muscle activity. Recently, three independent syntheses of the toxin have been reported [2,3,4] but each of these syntheses of the toxin suffers at least one disadvantage in the stereoselectively synthetic sense. This fact prompted us to investigate the stereoselective synthesis of pumiliotoxin C through a simple pathway.

An attempt was first made to convert the methoxy-nitriles, (2)[5] and (3)[5], into cis-decahydroquinol-2,7-dione (4). This attempt, however, was not successful due to resistance of the compounds towards demethylation. As a result, it was desired to synthesize a 1-hydroxy[2,2,2]octane derivative such as compound (9) which would be transformed readily into the cis-decahydroquinoline derivative (5) through the retro-aldol type bond cleavage and the subsequent intramolecular Michael type addition. For this purpose, 1,3-bis(trimethylsilyloxy)-5-methylcyclohexa-1,3-diene (6) would be most suitable as a diene component in the Diels-Alder reaction since facile removal of trimethylsilyl groups from the resulting cycloadduct could be expected.

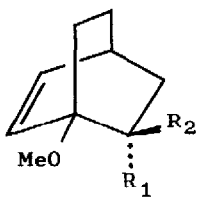
On the other hand, only two acyclic 1,3-dioxygenated 1,3-dienes[6,7] have been reported as diene components in the Diels-Alder reaction. We explored application of a new type diene, 1,3-bis(trimethylsilyloxy)-1,3-butadiene, to the present synthesis.

In the present communication, we wish to deal with the stereoselective synthesis of dl-pumiliotoxin C using novel 1,3-bis(trimethylsilyloxy)-1,3-dienes, 6 and 10.

The Diels-Alder reaction of 1,3-bis(trimethylsilyloxy)-5-methylcyclohexa-1,3-diene (6: bp. 92°/5 mm Hg, 82 % yield)*1, which was prepared from 5-methylcyclohexa-1,3-dione and trimethylsilyl chloride, with acrylonitrile

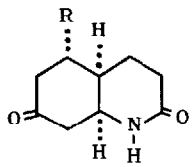


(1)



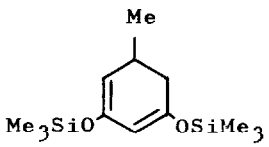
(2) R_1 = CN, R_2 = H

(3) R_1 = H, R_2 = CN

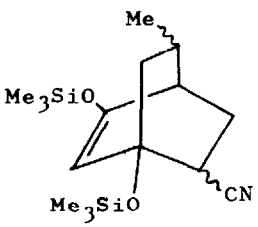


(4) R = H

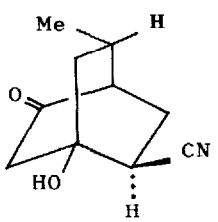
(5) R = Me



(6)



(7)



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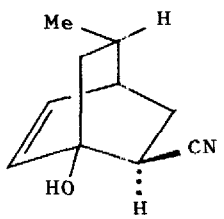

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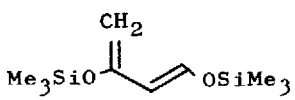
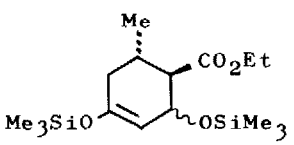
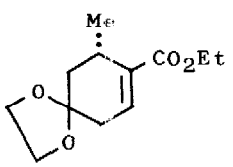


(10)



(11)



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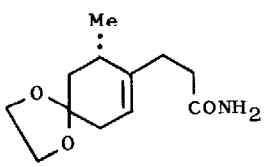

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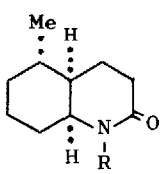
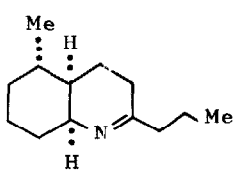


(14) R = H

(15) R = $CO(CH_2)_2Me$



(16)

gave a mixture of cycloadducts (7: 75 % yield). Because the cycloadducts were moisture-sensitive, the unpurified mixture (7) was directly treated with 10 % HCl at 0° to give the crystalline keto-nitrile (8: mp. 117°, $\nu_{max.}^{CHCl_3}$ 3430, 2250 and 1725 cm^{-1}, 51 % yield)*2 in a pure state. Successive treatments of the compound (8) with pyridinium hydrobromide perbromide, $NaBH_4$, and Zn-AcOH provided the exo-cyano compound (9: colorless oil, 64 % yield). Retrograde-aldol type bond fission of 9 using 15 % $HClO_4$-AcOH at 100° yielded the keto-lactam (5: mp. 197°, 37 % yield), a sample of which was identical in all respects with an authentic sample.[2]

Another synthetic route to the keto-lactam (5) involves the Diels-Alder reaction in which an acyclic 1,3-bis(trimethylsilyloxy)-1,3-diene is employed as a diene component. Thus, reaction of trans-1,3-bis(trimethylsilyloxy)-1,3-butadiene (10: bp. 58°/4 mm Hg) prepared from sodioacetoacetaldehyde[8] and trimethylsilyl chloride, with ethyl crotonate in xylene at 170° afforded the adduct (11: bp. 143°/5 mm Hg, 80 % yield) as a single product. This adduct was converted into the ketal-ester (12: bp. 119°/5 mm Hg, 87 % yield) by refluxing with ethylene glycol-p-TsOH in benzene. Successive treatments of 12 with $LiAlH_4$ (80 % yield), TsCl[9] (74 % yield), cyanomethylcopper[10] (80 % yield), and H_2O_2-aq. NaOH (80 % yield) afforded the ketal-amide (13: mp. 97°). Deketalization of 13 with 1 % HCl and the subsequent cyclization reaction with NaOMe in methanol*3 gave the keto-lactam (5: mp. 197°, 63 % yield) as a thermodynamically stable product.

The keto-lactam (5), synthesized through the two routes mentioned above, was transformed into the lactam (14: mp. 152°, 76 % yield from 5) by a method previously reported.[2] Treatments of the lactam (14) with NaH-butyryl chloride in THF-HMPA mixture gave the N-butyryl compound (15: colorless oil, 90 % yield) which afforded the imine (16: colorless oil, 18 % yield) on heating with CaO.[11]

Finally, catalytic hydrogenation of the imine (16) in 2N-HCl over PtO_2 gave dl-pumiliotoxin C (1: colorless oil, quantitative yield). No stereoisomer was detected by GLC (1.5 % SE 30 column, 2 m, 150°).

dl-Pumiliotoxin C hydrochloride (mp. 232°) derived from the free base, was identical in all respects with an authentic sample previously synthesized by the authors.[2]

Because of the ready preparation of 1,3-bis(trimethylsilyloxy)-1,3-butadiene, especially its alkyl-substituted derivatives and the ease of removal of trimethylsilyl group, these dienes may find value as diene components in the Diels-Alder reaction.

FOOTNOTES AND REFERENCES

*1 All compounds reported in this communication gave satisfactory i.r., n.m.r., and microanalysis or mass spectral data.

*2 The stereochemistry of the bicyclo[2,2,2]octane derivatives, 8 and 9, will be presented in a separate paper.

*3 Cyclization reactions with various acids also gave product (5) in a very low yield.

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