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SYNTHESIS OF AN ADVANCED QUINOCARCIN INTERMEDIATE FROM L-GLUTAMIC ACID

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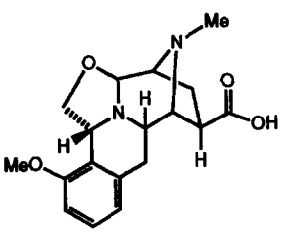
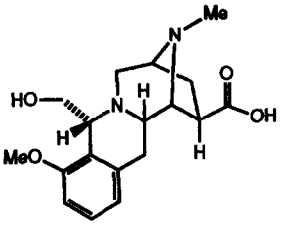
Summary: A key intramolecular N-acyliminium ion/silylenol ether cyclization of **17**, derived from L-glutamic acid, has been used to construct the bridged bicyclic quinocarcin intermediate **3**.

Quinocarcin (**1**), a novel antitumor antibiotic produced by Streptomyces melanovinaceus,[1] co-occurs with a related inactive metabolite quinocarcinol (**2**). Several research groups have recently described approaches to these compounds,[2] including a total synthesis of quinocarcinol methyl ester by Danishefsky, et al.[3] and a total synthesis of racemic quinocarcin by Fukuyama and Nunes.[4] We now report a stereoselective synthesis of bicyclic lactam **3** in chiral form. This compound is closely related to silyl ether protected compound (±)-**4**, an intermediate in the Fukuyama quinocarcin synthesis.[4]



1



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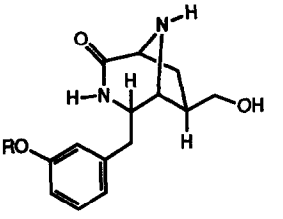
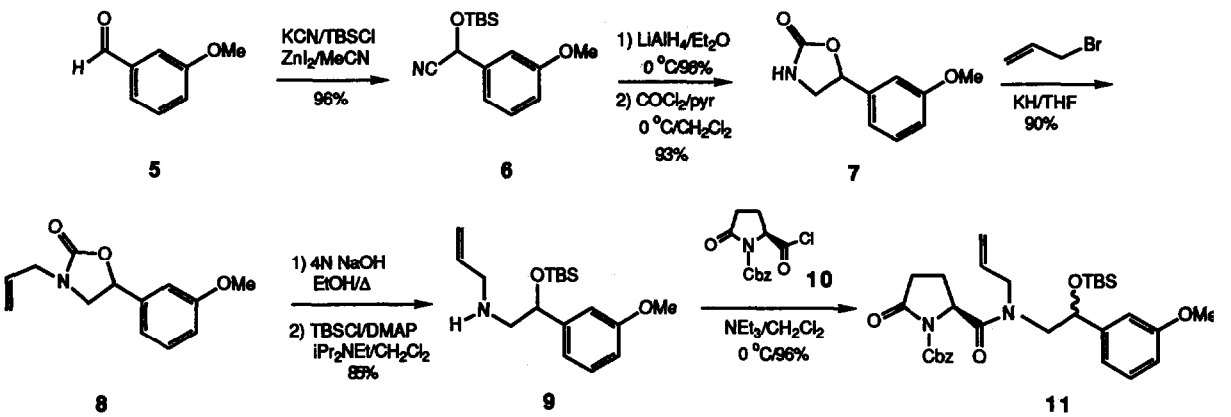


3 R = Me
4 R = DMTS

Our synthesis of **3** began with m-anisaldehyde (**5**) which was converted to siloxy nitrile **6** using the Cava procedure[5] (**Scheme 1**). This compound was reduced to the amino alcohol and converted to cyclic carbamate **7**. N-Allylation of **7** produced compound **8** and subsequent hydrolysis of the carbamate functionality followed by O-silylation gave amine **9** in high overall yield from aldehyde **5**. Condensation of **9** with readily available acid chloride **10**, prepared in optically pure form from L-glutamic acid,[6] afforded amide **11** in excellent yield.

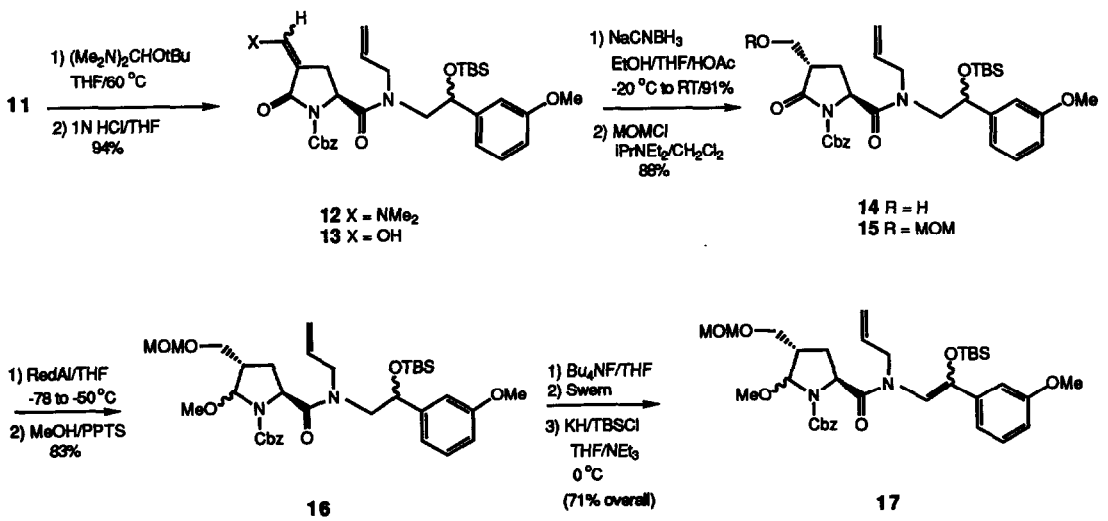
Scheme 1



To continue the synthesis, lactam **11** was combined with Bredereck's reagent[7,8] to produce enamine **12** (**Scheme 2**). Without purification, **12** was cleanly hydrolyzed with acid to hydroxymethylene lactam **13**. Reduction[9] of **13** with sodium cyanoborohydride, presumably via the aldehyde tautomer,[10] gave the desired trans alcohol **14** along with the cis isomer in an 8:1 ratio. The hydroxyl group of **14** was then protected to give the MOM ether **15**.

It was possible to chemoselectively reduce the lactam carbonyl functionality of **15** with RedAl at low temperature, followed by treatment of the crude product with methanol/PPTS, to

Scheme 2

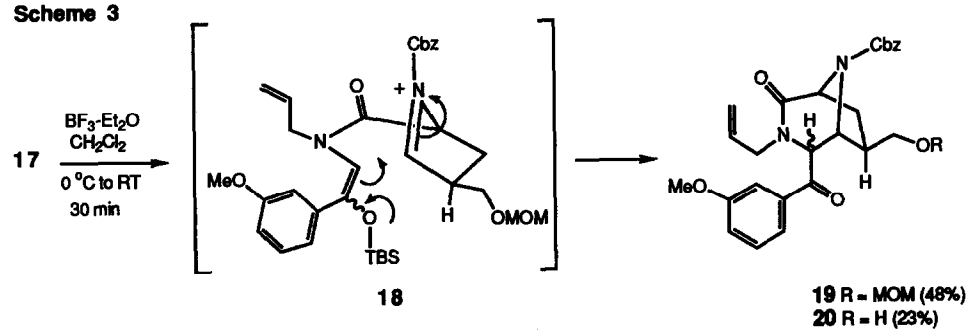


afford methoxy carbamate **16**. This intermediate was converted in three simple steps to a mixture of E and Z silylenol ethers **17**.

The key transformation in our synthetic approach was envisioned to be cyclization of silylenol ether **17** to form the requisite bridged system of **3**. Treatment of compound **17** with

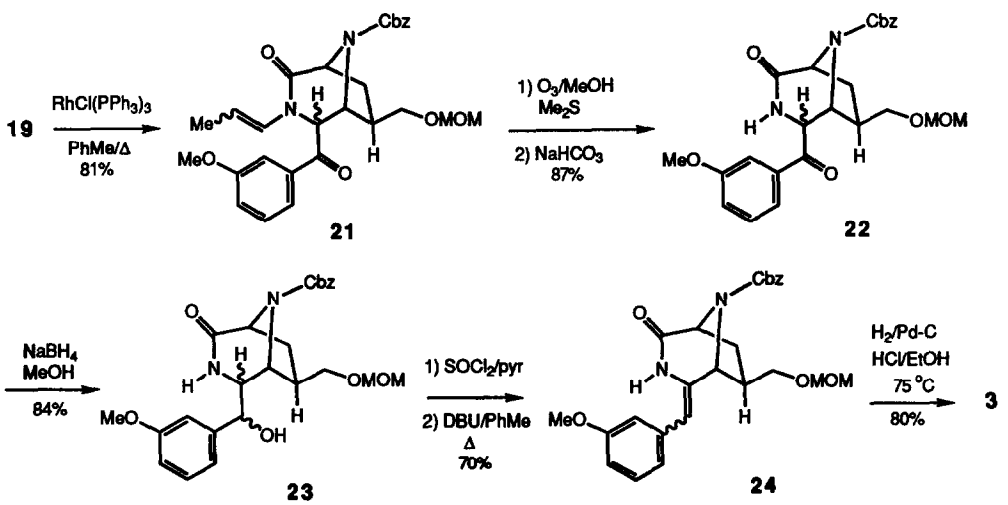
boron trifluoride etherate in fact produced the desired bicyclic lactam **19** (48%) along with some of the deprotected alcohol **20** (23%) (**Scheme 3**). Both cyclization products were 2:1 mixtures of epimers adjacent to the benzoyl group. This step probably occurs via the N-acyliminium intermediate **18**.[11,12,13]

Scheme 3



Correlation of lactam **19** with Fukuyama's quinocarcin intermediate **4** was accomplished as shown in **Scheme 4**. The N-allyl protecting group of **19** was removed by rhodium promoted isomerization to ene lactam **21**, followed by ozonolysis and mild basic hydrolysis of the resulting N-formyl lactam, providing keto lactam **22**. Reduction of **22** afforded a mixture of diols **23** which was dehydrated to a mixture of E/Z olefins **24**. Finally, hydrogenation of **24** under acidic conditions stereoselectively reduced the alkene moiety with concurrent removal of the Cbz and MOM protecting groups, yielding amino alcohol **3**. The spectra of compound **3** were very similar to those of **4**.[14]

Scheme 4



Thus, we have devised a stereoselective approach to quinocarcin intermediate **3** starting from inexpensive, optically pure L-glutamic acid. It should be possible to convert **3** to (-)-quinocarcin using the chemistry developed by Fukuyama.[4]

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8. In a similar system, Danishefsky and coworkers found that the Bredereck reaction could be effected without racemization of the pyroglutamate moiety: Danishefsky, S.; Berman, E.; Clizbe, L.A.; Hirama, M. J. Am. Chem. Soc. **1979**, 101, 4385.
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10. The ^{1}H NMR spectrum of **13** shows the presence of a small amount of the aldehyde.
11. For a recent review of intramolecular N-acyliminium ion cyclizations see: Hiemstra, H.; Speckamp, W.N. in "The Alkaloids"; Brossi, A., Ed.; Academic Press, New York, **1988**; Vol. 32, p. 271.
12. The cyclizations of the E and Z silylenol ether isomers of **18** may be stereospecific, but we have been unable to separate the geometric isomers of **17** and thus have not been able to test this point.
13. ^{1}H NMR analysis of a derivative of one isomer of **20** (R = Ac) lacking the Cbz group with $Eu(hfc)_3$ showed it to be a single enantiomer ($[\alpha]_D^{23} = +44^{\circ}$ (c = 0.055, $CHCl_3$).
14. We are extremely grateful to Professor Tohru Fukuyama (Rice University) for providing copies of spectra of **4** and related synthetic compounds.

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