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Stereoselective Synthesis of Penaresidin A and Related Azetidine Alkaloids

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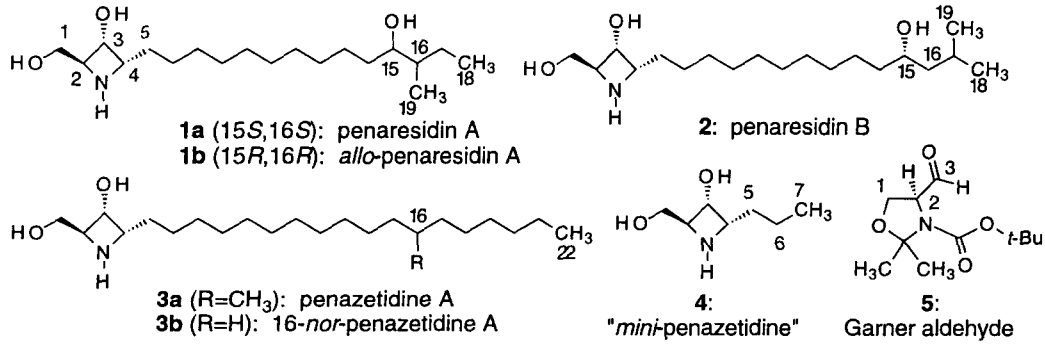
Abstract: *Several sphingosine-like azetidine alkaloids have been synthesized from the Garner aldehyde 5, including the ATPase activator penaresidin A (1a), its side chain isomer 1b, and the 16-nor analogue (3b) of the protein kinase C inhibitor penazetidine A 3a.* © 1997 Elsevier Science Ltd.

Azetidine-containing alkaloids are rare,[1] but two recent reports describe the isolation of biologically active sphingosine-like compounds from marine organisms. In 1991, the novel alkaloids penaresidin A (**1a**) and B (**2**) were isolated as a mixture from the Okanawan sponge *Penares* sp.[2] Tested as the mixture,[2] these compounds elevated the ATPase activity of myofibrils from rabbit skeletal muscle to 181% of control at 3 X 10^{-5} mol dm^{-3}. The structures, particularly with respect to the side-chain absolute stereochemistry, were established by spectroscopic methods[2] supplemented by synthetic studies.[3-5] In 1994, Crews and coworkers reported a related compound, penazetidine A (**3a**), which they had discovered by screening extracts of the Indo-Pacific marine sponge *Penares sollasi* for protein kinase C inhibitory activity.[6] With an IC_{50} = 1 μM, **3a** is one of only a few compounds to show specific rat brain PKCβ1 inhibition (but compare staurosporine, IC_{50} = 6 X 10^{-10} M; as control for **3a**, 100% inhibition at 0.1 μM).[6] Its structure, except for the side-chain stereochemistry, was confirmed by synthesis in 1996.[7]

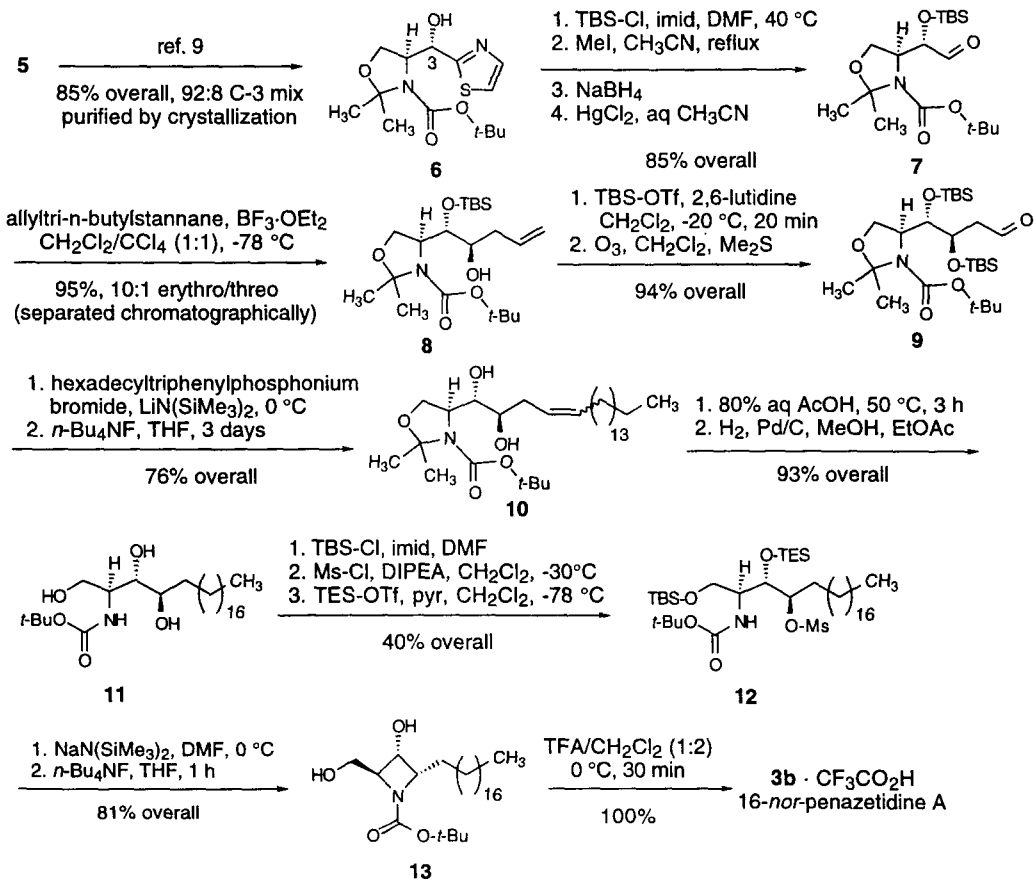
To lay a foundation for broader biological evaluation and for structure/activity studies, we undertook the synthesis of this class of azetidine alkaloids. We report the stereoselective synthesis of four representatives: penaresidin A (**1a**), its side chain isomer **1b**, 16-*nor*-penazetidine A **3b**, and the "mini-penazetidine" **4**.



The synthesis of 16-*nor*-penazetidine A (**3b**) is shown in Scheme 1. Garner aldehyde **5**[8] was chain-extended by the method of Dondoni[9,10] to provide hydroxy-thiazole **6** as the 3(*S*) isomer following crystallization. Conversion to aldehyde **7**[11] was followed by stereoselective Keck allylation,[12] giving the adduct **8** as a pure diastereomer after chromatography. The unusual solvent combination of 1:1 CCl_4/CH_2Cl_2 improved the stereoselectivity to 10:1, compared with 4:1 in CH_2Cl_2, perhaps because of tightening of the

Lewis acid-base pair. Protection of the secondary hydroxyl and then ozonolysis gave the six-carbon aldehyde **9**, which was chain-extended by Wittig reaction. Removal of the silyl protecting groups gave the alkene **10** as a mixture of *cis* and *trans* isomers. Selective hydrolysis[13] of the N,O-acetonide and then hydrogenation gave triol **11**, which was prepared for cyclization by selective protection of the primary hydroxyl, selective mesylation of the less hindered secondary hydroxyl, and finally protection of the remaining hydroxyl as its triethylsilyl ether. The resulting substrate **12** was smoothly cyclized to the azetidine by treatment with sodium hexamethyldisilazide. Desilylation gave the diol **11**, and then removal of the N-*tert*-butoxycarbonyl group afforded 16-*nor*-penazetidine A **3b** as its trifluoroacetate salt. The structure and stereochemistry were confirmed by comparing the ^{1}H and ^{13}C NMR spectra of synthetic **3b** and those reported for penazetidine A **3a**.[6]

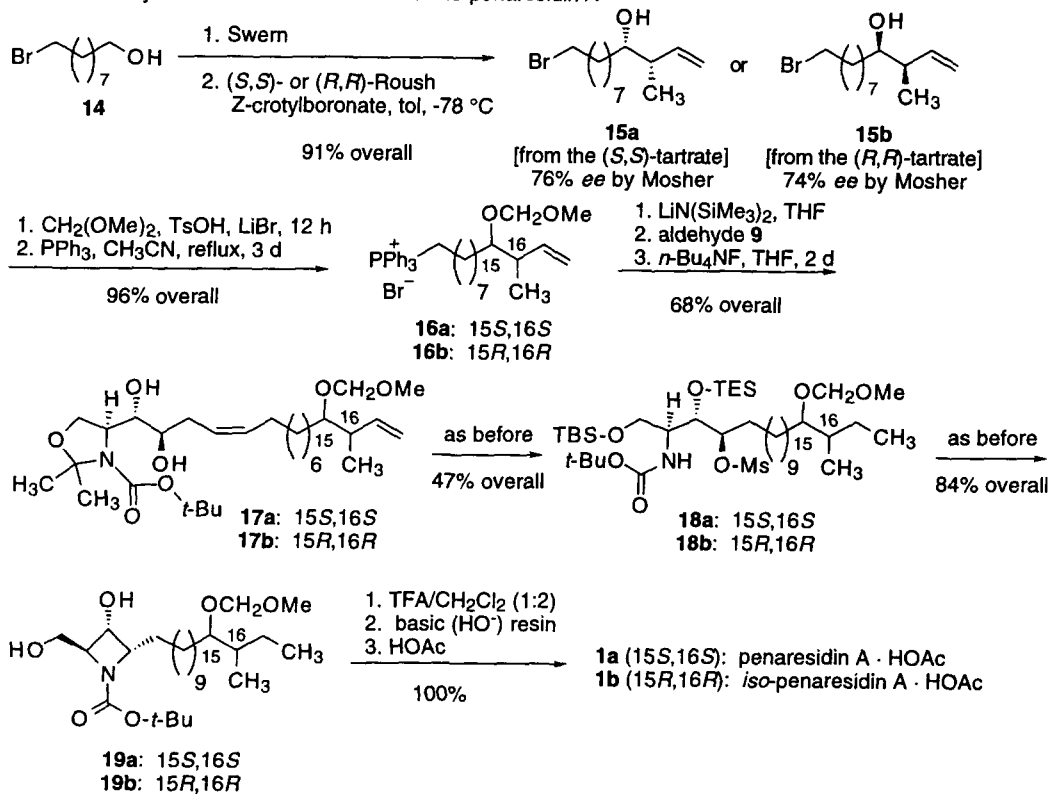
Scheme 1. Synthesis of 16-*nor*-Penazetidine A



Scheme 2 shows the synthesis of penaresidin A (**1a**, **a**-series) and *allo*-penaresidin A (**1b**, **b**-series). Yields shown are for the **a**-series, but **b**-series yields were comparable. The side chains were assembled by oxidation of commercially available 9-bromononanol (**14**), followed by addition of the Roush tartrate-based *Z*-

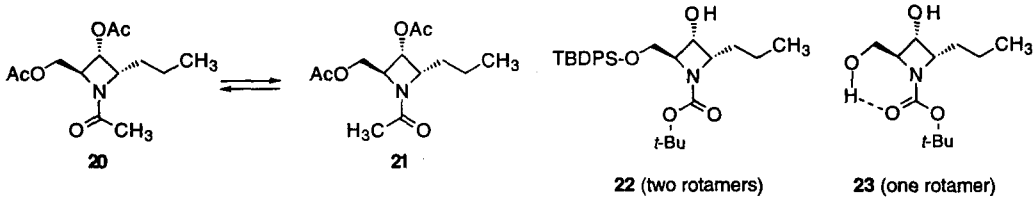
crotylboronates: (*S*,*S*) for adduct **15a**, (*R*,*R*) for adduct **15b**.[14] Syn adducts were obtained with high stereoselectivity; the enantioselectivity in each case was established as approximately 75% *ee* by ^{1}H NMR analysis of the derived (*S*)-MTPA Mosher esters.[15] The bromo alcohols **15** were protected as O-methoxymethyl ethers and then converted to Wittig reagents **16**. Chain extension of aldehyde **9** and then desilylation led to the *cis*-alkenes **17**, which were further converted to cyclization substrates **18** and then cyclized to azetidines **19** by using transformations analogous to those in Scheme 1. Simultaneous N-BOC and O-MOM removal followed by treatment with basic resin and then acetic acid gave penaresidin A (**1a**) and its diastereoisomer **1b** as acetate salts. Confirmation of **1a** as the natural product was achieved by separately analyzing the 500-MHz ^{1}H NMR spectra of its N-acetyl-O,O,O-tris[(*S*-) and (*R*)-methoxy(trifluoromethyl)-(phenyl)acetyl] derivatives and matching them exactly with the reported values[4] of the corresponding (*S*-) and (*R*)-Mosher derivatives of natural **1a**. Furthermore, the corresponding (*S*)-Mosher derivative of **1b** showed an H-15 signal that is clearly different from that of the (*S*)-Mosher derivative of **1a** (δ 4.86 vs 5.07, respectively), although the spectra are otherwise indistinguishable.[16]

Scheme 2. Synthesis of Penaresidin A and *allo*-penaresidin A



The truncated version of **3a**, "*mini*-penazetidine" **4**, was prepared from homoallylic alcohol **8** by hydrogenation and then processing as for **10** → **3b**. An unsaturated 4-mesylate derived from **8** could not be cyclized to the azetidine because of competing E2 elimination to afford the conjugated diene. As a result, azetidine formation had to follow side chain elongation in all routes.

An interesting rotameric situation arises for the N-acyl-(hydroxymethyl)azetidines and their O-protected derivatives. The N,O,O-triacetate derivative of mini-penazetidine **4** exhibits two amide rotamers in the ^{1}H NMR spectrum (**20** and **21**), as had been reported for the analogous derivatives of **1a** and **1b**.[3] BOC-azetidine **22** also shows two rotational isomers. However, the N-BOC diol **23** shows a single rotational isomer in $CDCl_3$ solution, and a deshielded primary (by decoupling) hydroxyl proton at δ 4.65 (br d, J = 6.4). This may be attributed to a stable intramolecular hydrogen bond to the N-BOC carbonyl, as illustrated below.



Acknowledgments. We are grateful to American Cyanamid, Berlex, and Hoffmann-La Roche for financial support of this work. YD also thanks Berlex for a summer research fellowship.

References and Notes

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16. A small amount of the (*S*)-Mosher derivative of N-acetyl-**1b** contaminates the corresponding derivative of **1a** (and vice versa), as anticipated by the Mosher analysis of side-chain stereochemistry (see **15a/15b**).

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