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A highly stereoselective approach to novel 2,2,4-trisubstituted pyrrolidines by halocylization: key intermediates towards syntheses of nitrogen analogs of Noxafil®

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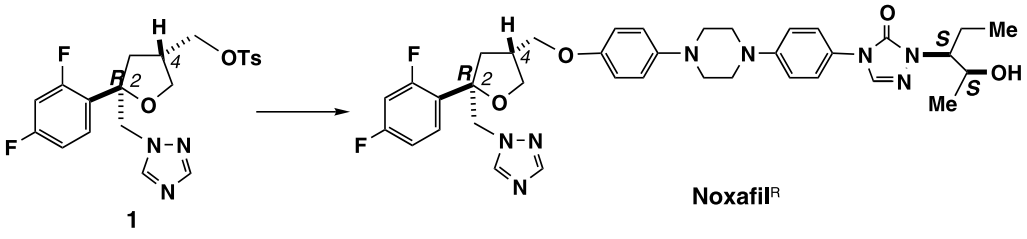
Abstract—A convenient synthesis of novel 2,2,4-trisubstituted pyrrolidines via stereoselective 5-*exo* iodocyclization of the 2,2-disubstituted olefins **8** and **9** is described. Single crystal X-ray analysis of the oxazolidinone **15** confirmed the relative stereochemistry in this cyclization. As observed earlier in the formation of 2,2,4-trisubstituted tetrahydrofurans, the presence of a bulky aryl substituent on the olefin appears to direct the stereochemical outcome of these halocyclizations.

Noxafil® is a novel 2,2,4-trisubstituted tetrahydrofuran based antifungal agent currently undergoing late-stage phase III clinical trials. It has shown improved therapeutic potential over existing drugs against a variety of invasive fungal infections in normal and immunocompromised patients refractory to or intolerant of standard therapy.[1] Halocyclization provides an effective methodology for stereoselective construction of substituted tetrahydrofurans. Recently we described the enantioselective synthesis of (−)-2*R*-*cis*-tosylate **1**, which acted as a central intermediate towards Noxafil® and a variety of highly active analogs.[2] Synthesis of **1** was accomplished in a highly stereoselective manner via a novel 2,4-diastereoselective halocyclization of an optically active 2,2-disubstituted δ-olefin.[2c]

A logical extension would be to prepare the nitrogen analog of this important therapeutic agent by replacement of the 2,2,4-trisubstituted tetrahydrofuran core with a pyrrolidine moiety. Examples dealing with stereoselective electrophilic cyclization of unsaturated nitrogen compounds from acyclic precursors are relatively few compared to the analogous oxygen cases.[3,4] Mercury or selenium induced intramolecular cyclizations of amido or amino precursors have been reported to provide mainly 2,5-disubstituted pyrrolidines with good stereocontrol.[5] An elegant stereoselective approach to 2,5-*trans* or 2,5-*cis* pyrrolidines, via overall 5-*endo*-trig iodocyclization of homoallylic tosylamides, was recently described.[6] A careful search of the literature led us to conclude that no example existed of stereoselective halocyclizations leading to 2,2,4-trisubstituted pyrrolidines such as **10**–**13**.[7,8]

The olefinic homochiral diol **2**, readily available from a previous study,[2c] was converted to the benzylidine



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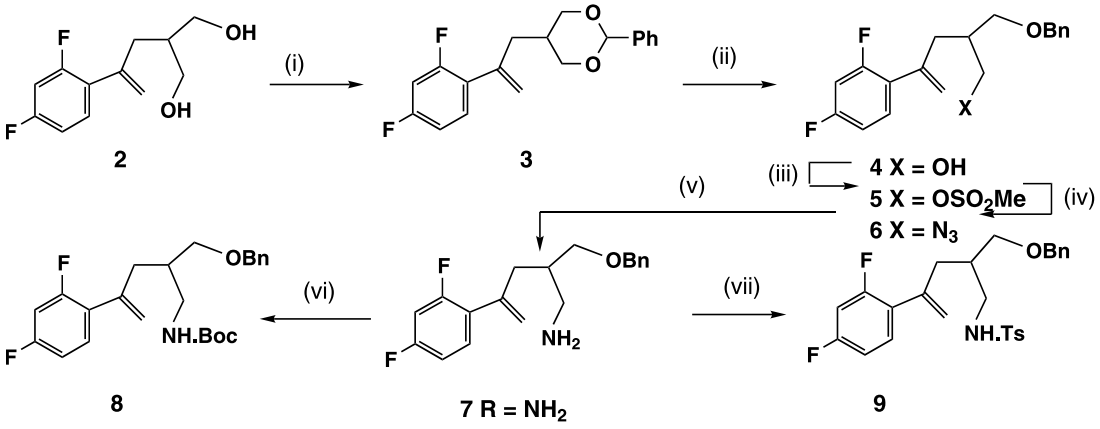
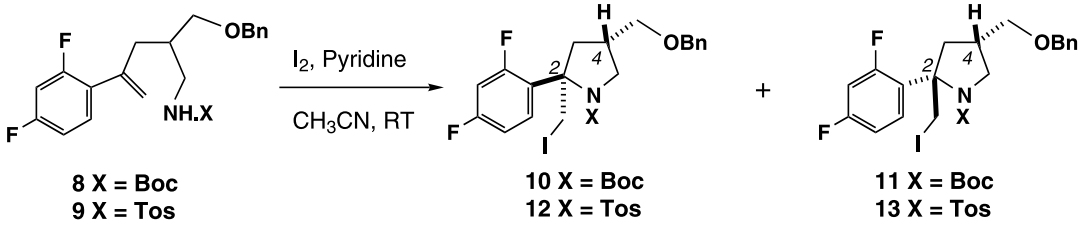
acetal **3**. Reduction of **3** with diisobutylaluminiun hydride (DIBAL) provided the monobenzyl alcohol **4** in 94% yield over two steps. Attempted direct displacement of the hydroxyl group in **4** with diphenylphosphorylazide (DPPA) failed to provide the azide **6**. However, conversion of the alcohol **3** to the mesylate **5** followed by displacement with sodium azide provided the desired azide **6** in 50% yield over two steps. Lithium aluminium hydride (LAH) reduction of **6** and treatment of the resulting amine **7** with di-*tert*-butyl dicarbonate or *p*-toluene sulfonyl chloride provided the *N*-Boc and *N*-tosyl protected amines **8**[9] and **9**[10] in 89 and 92% yield, respectively (Scheme 1).

Iodocyclization of the protected amino alcohols **8** and **9**, under irreversible conditions proceeded in excellent yields and 2,2,4-diastereoselectivity to provide **10**/**11**[11] and **12**/**13**[12] as *cis*:*trans* mixtures. The major isomers in both cases were *cis* with respect to the iodomethyl and benzyloxymethyl functionalities. Presumably due to the greater steric bulk imposed by the *t*-butyl group, the *cis*:*trans* ratio of the cyclized product from **8** was superior (**10**:**11**, >95:5; 88% yield) compared to the cyclized products from **9** (**12**:**13**, 83:17; 72% yield). This bias in favor of the *cis* isomers did not change in the absence of base (Scheme 2).

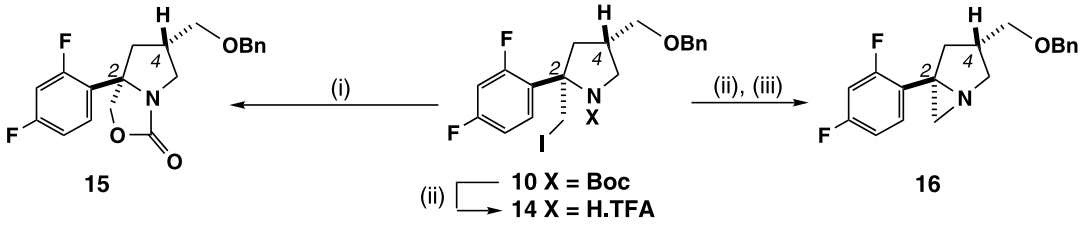
Since **10**/**11** existed as rotamer mixture, removal of the *N*-Boc group with trifluoroacetic acid was employed to give the amine salt **14** from which the *cis*:*trans* isomer ratio could be accurately determined by NMR. NOE experiments on **14**[13] showed independently that the iodomethyl and benzyloxymethyl groups are *cis* to each other. In contrast to the corresponding tetrahydrofurans,[2] not surprisingly direct displacement of iodine even by the highly nucleophilic triazolyl anion with either *N*-Boc or *N*-tosyl protected pyrrolidines proved challenging. Thus treatment of **10** with Na-1,2,4-triazole at elevated temperature, afforded the crystalline oxazolidone **15**,[14] mp 78–80°C (Scheme 3). Treatment of **14** with aqueous $NaHCO_3$ in a one-pot sequence provided the aziridine **16** as a yellow oil (~90% yield).



Scheme 1. *Reagents and conditions*: (i) $PhCH(OMe)_2$, PPTS, DMF, rt; (ii) DIBAL, benzene–hexane, rt; (iii) MsCl, Et_3N, CH_2Cl_2, 0–5°C; (iv) NaN_3, DMF, 80°C; (v) LAH, EtOEt, rt; (vi) Boc_2O, CH_2Cl_2, rt; (vii) TsCl, pyridine, CH_2Cl_2, 0–5°C.



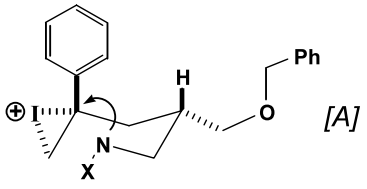
Scheme 2.

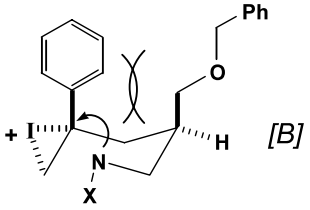


Scheme 3. *Reagents and conditions*: (i) Na-triazole, DMF, 60°C, 24 h; (ii) TFA, CH_2Cl_2, rt; aq. $NaHCO_3$.

The crystal structure of **15** was solved by direct methods (MULTAN 11/82)[15] (Fig. 1). The asymmetric unit consists of two molecules. Approximate coordinates for the non-hydrogen atoms were derived in part from an *E*-map and from a series of weighted F_o and difference Fourier syntheses phased successively by an increasing number of atoms. Positional and thermal parameters of these atoms (first isotopic and then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations. Hydrogen atoms were incorporated at their calculated positions, and an extinction correction was included as a variable during the later cycles. A final difference Fourier synthesis contained no unusual features.

The observed 2,4-distereoselectivity in the present examples is consistent with the rationale that we proposed ealier for the stereoselective formation of 2,2,4-trisubstituted tetrahydrofurans.[2c] In a chairlike transition state first proposed by Harding and Burks[16] for the amidomercuration of olefinic amides, equatorial disposition of the 4-aminomethyl substituent as depicted in [A] may account for the major **10** and **12** type products. A minor pathway such as [B] will have unfavorable steric repulsion between the 2-aryl and the axially disposed 4-hydroxymethyl substituents.





In conclusion we have demonstrated a simple and highly stereoselective synthesis of 2,2,4-trisubstituted pyrrolidines **10** and **12**. These and derived key intermediates **15** and **16** offer further opportunities for a variety of selective transformations possibly leading up to analogs of Noxafil® and other biologically interesting compounds.

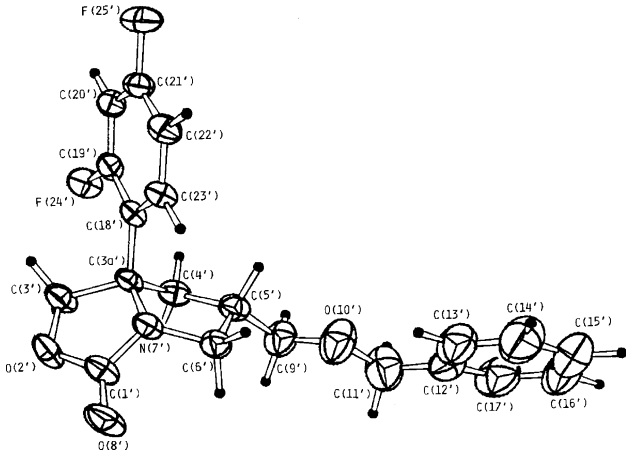


Figure 1.

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7. *Procedure for the synthesis of **10***: An acetonitrile solution of **8** was cooled to 0°C and treated with pyridine (42 μL, 2.1 equiv.) followed by iodine (126 mg, 2.0 equiv.). The solution was shielded from light and stirred at rt overnight (16 h) TLC indicated that a small amount starting material was left. The reaction mixture was treated with $Na_2S_2O_3$ (aq.) solution until the purple color faded. The mixture was diluted with EtOAc and washed with water and brine. The crude product was purified on silica gel column using 10% Ethyl acetate/hexane as eluent to afford the cyclized product **10** (118 mg, 88%, clear oil). The NMR experiments showed that **10** existed in rotamers. Removal of the Boc group resulted in predominantly the *cis* product from which the ratio of *cis*/*trans* isomers was determined.
8. All new compounds were characterized by ^1H, ^{13}C, NMR and high resolution mass spectra. When necessary 1D NOE and 2D NOESY NMR spectra were obtained to confirm relative stereochemistry. Elemental analysis were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selective spectral data is given here.

9. **8**: FAB-MS m/z 418 (M+H), 362 (M–Bu+H), 318 (M–Boc, 100%). ^{1}H NMR [300 MHz, $CDCl_3$] δ 1.42 (s, 9H), 1.79 (m, 1H), 2.50 (m, 2H), 3.12 (m, 1H), 3.25 (m, 1H), 3.37 (dd, $J=4.2$, 9.2 Hz, 1H), 3.42 (dd, $J=4.5$, 9.4 Hz, 1H), 4.44 (s, 2H), 4.95 (bs, 1H), 5.18 (s, 1H), 5.22 (s, 1H), 4.79 (m, 2H), 7.30 (m, 6H).
10. **9**: FAB-MS m/z 472 (M+H, 100%), 380 (M–CH_2Ph, 366 (M–OCH_2Ph), 316 (M–Ts). ^{1}H NMR [300 MHz, $CDCl_3$] δ 1.75 (m, 1H), 2.42 (s, 3H), 2.44 (d, $J=11$ Hz, 2H), 2.90 (m, 1H), 3.05 (m, 1H), 3.28 (dd, $J=6.0$, 8.3 Hz, 1H), 3.41 (dd, $J=3.8$, 9.3 Hz, 1H), 4.39 (s, 2H), 5.14 (s, 2H), 5.17 (s, 1H), 5.24 (t, $J=6.0$ Hz, 1H), 6.78 (m, 2H), 7.10 (m, 1H), 7.30 (m, 7H), 7.65 (d, $J=9.0$ Hz, 2H).
11. **10**: CI-MS m/z 544 (M+H), 488 (M–Bu+H), 444 (M–Boc, 100%), 360 (M–I). ^{1}H NMR [300 MHz, $CDCl_3$] δ 1.37 (s), 1.40 (s), 2.24 (m), 2.65 (m), 3.08 (m), 3.25 (m), 3.47 (m), 3.80 (m), 4.07 (d, $J=10$ Hz), 4.22 (m), 4.50 (s), 4.54 (d, $J=10$ Hz), 6.78 (m), 7.10 (m), 7.30 (m).
12. **12**: CI-MS 598 (M+H), 490 (M–BnOH), 470 (M–I), 456 (M–CH_2I), 442 (M–Ts), 380 (M–Bn–I), 315 (M–Ts–I). *cis*-Isomer: ^{1}H NMR [400 MHz, $CDCl_3$] δ 2.4 (s, 3H), 2.65 (m, 1H), 3.45 (m, 2H), 3.94 (t, $J=8.7$ Hz, 1H), 4.22 (d, $J=10.7$ Hz, 1H), 4.38 (d, $J=10.7$ Hz, 1H), 4.50 (s, 2H), 6.57 ddd, $J=2.6$, 8.5, 10.7 Hz, 1H), 6.90 (ddt, $J=1.0$, 2.7, 8.7 Hz, 1H), 7.19 (d, $J=8.1$ Hz, 2H), 7.31 (m, 1H), 7.45 (d, $J=8.3$ Hz, 2H), 7.75 (dt, $J=6.2$, 9.1 Hz, 1H).
13. **14**: FAB-MS m/z 444 (M+H), 316 (M–I, 100%). ^{1}H NMR [300 MHz, $CDCl_3$] δ 2.41 (dd, 1H), 2.76 (m, 1H), 2.95 (dd, 1H), 3.55 (m, 4H), 3.90 (AB, 2H), 4.55 (AB, 2H), 6.98 (m, 1H), 7.35 (m, 6H).
14. **15**: FAB-MS m/z 360 (M+H, 100%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 1.89 (dt, $J=1.8$, 12.1 Hz, 1H), 2.44 (m, 2H), 3.44 (d, $J=5.8$ Hz, 2H), 3.50 (dd, $J=8.5$, 11.7 Hz, 1H), 3.64 (dd, $J=6.9$, 11.7 Hz, 1H), 4.27 (d, $J=9.2$ Hz, 1H), 4.49 (s, 2H), 4.68 (dd, $J=2.3$, 9.1 Hz, 1H), 6.88 (m, 2H), 7.30 (m, 6H).
15. Atomic parameters, bond lengths, bond angles and torsion angles for **15** have been deposited at the Cambridge Crystallographic Data Center, Cambridge, CB2 1EZ, UK. Any request should be accompanied by full literature citation for this communication.
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