ENANTIOSELECTIVE SYNTHESIS OF INDOLIZIDINE ALKALOID: A FORMAL TOTAL SYNTHESIS OF (-)-PUMILIOTOXIN 251D

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Abstract---An enantioselective formal total synthesis of (-)-pumiliotoxin 251D was achieved by employing the Sharpless kinetic resolution of the 2-furylmethanol derivative (**3**) and a stereoselective radical cyclisation of the thiocarbonyl-imidazolide (**10**) as key steps .

Indolizidine alkaloids possessing the 1-azabicyclo[4.3.0]nonane skeleton are widely distributed in nature with their wide range of structural and stereochemical features. Due to their interesting biological properties, this class of alkaloids have provoked an extraordinary amount of activity by synthetic organic chemists.[1] Recently, Gallagher and his co-workers have published[2] the elegant total synthesis of (-)-pumiliotoxin 251D (**1**) *via* the lactam (**24**) and this report has prompted us to disclose our efforts directed toward the synthesis of **1** (Figure 1).

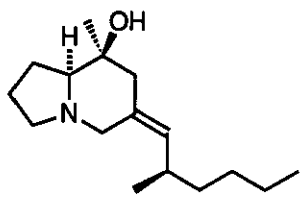

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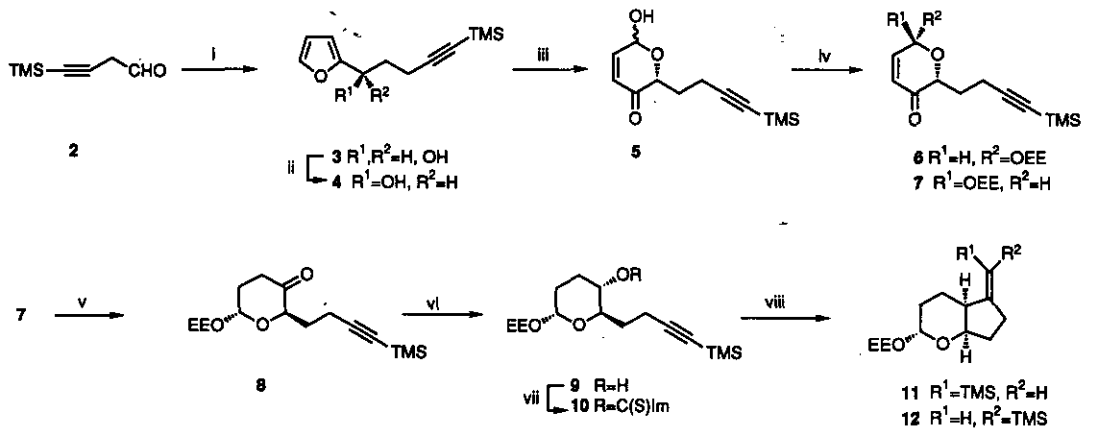
Figure 1

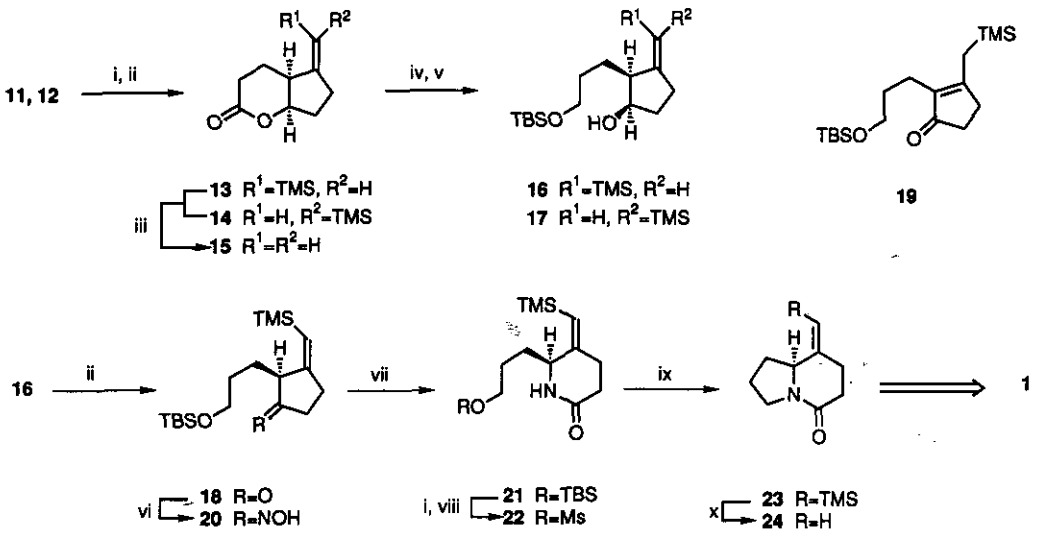
The synthesis that we have developed involves the Sharpless kinetic resolution using L-di-isopropyl tartrate, titanium tetraisopropoxide, and *tert*-butyl hydroperoxide, of the racemic 2-furylmethanol derivative (**3**),[3] readily derived from 2-lithiofuran and 5-trimethylsilyl-4-pentyn-1-al (**2**), providing the *R*-alcohol (**4**) in 46.5% yield with >95% enantiomeric excess,[4] as a starting material. Oxidation of **4** with *N*-bromosuccinimide in aqueous tetrahydrofuran[5] afforded the lactol (**5**) in 98% yield, which on treatment with ethyl vinyl ether and pyridinium *p*-toluenesulphonate was converted into the ethoxyethyl ethers (**6**) and (**7**) in 93% yield in a ratio of 1:2.4. Reduction of the major isomer (**7**) with lithium aluminium hydride in the presence of copper(I) iodide[6] in tetrahydrofuran-hexamethylphosphoric triamide

(4:1,v/v) gave the 1,4-reduction product (**8**) in 70% yield. Further reduction of **8** with sodium borohydride provided the alcohol (**9**) as a major isomer, which was then transformed into the thiocarbonylimidazolide (**10**) in a usual manner[7] in 71% overall yield (Scheme 1).



Scheme 1 *Reagents and conditions*: i, 2-lithiofuran, THF, -78°C; ii, L-DIPT, $Ti(O^iPr)_4$, , TBHP, MS 3A, CH_2Cl_2, -25°C; iii, NBS, THF-H_2O (4:1), 0°C; iv, CH_2=CHOEt, PPTS, CH_2Cl_2; v, $LiAlH_4$, CuI, THF-HMPA (4:1), -78°C; vi, $NaBH_4$, THF, 0°C; vii, Im_2C=S, $ClCH_2CH_2Cl$, reflux; viii, Bu_3SnH, AIBN, benzene, reflux

We envisioned construction of the chiral indolizidine skeleton from the corresponding chiral 2-substituted cyclopentan-1-one, *via* the piperidone derivative, by using the Beckmann rearrangement with retention of the chiral center, followed by an intramolecular alkylation. Thus, treatment of the imidazolide (**10**) with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile in refluxing benzene afforded the cyclisation products (**11**) and (**12**) in 84% yield in a ratio of 4:3 as an inseparable mixture, which were further converted to the lactones (**13**) and (**14**) by deprotection of the ethoxyethyl group, followed by oxidation of the resulting lactols with pyridinium chlorochromate in 54% and 41% yields, respectively. The stereochemistry of **13**[8] was assigned as depicted in Scheme based on NOEs between the olefinic proton and one of the angular protons and also between two angular protons. Since desilylation of both compounds (**13**) and (**14**) with *p*-toluenesulphinic acid[9] in aqueous acetonitrile yielded the same olefin (**15**), the lactone (**14**) was unambiguously determined to the olefinic isomer of **13**. These results indicated that the radical cyclisation of **10** proceeded in a stereoselective manner to form the *cis*-ring juncture predominantly and none of the *trans* isomer could be isolated in this cyclisation. Lithium aluminium hydride reduction of **13**, followed by selective protection of the primary alcohol with *tert*-butyldimethylsilyl chloride gave the silyl ether (**16**), in 86% yield, which on oxidation with pyridinium chlorochromate in the presence of sodium acetate in dichloromethane afforded the desired chiral cyclopentanone (**18**) in 60% yield. Similar oxidation of **17**, prepared from **14** by two-steps as above, furnished the cyclopentenone (**19**) unfortunately (Scheme 2).



Scheme 2 *Reagents and conditions* : i, 2N HCl, THF, 0°C; ii, PCC, AcONa, CH_2Cl_2; iii, *p*-$MeC_6H_4SO_2H$, aq. MeCN; iv, $LiAlH_4$, Et_2O; v, TBSCl, Et_3N, CH_2Cl_2, 0°C; vi, NH_2OH•HCl, pyridine, MeOH; vii, $SOCl_2$, THF, 0°C; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; ix, K_2CO_3, dioxane-H_2O (4:1), 90°C; x, *p*-$MeC_6H_4SO_2H$, aq. MeCN, reflux.

With the requisite chiral cyclopentanone available, a study was made of the best condition for the Beckmann rearrangement of the corresponding oxime (**20**) to the piperidone (**21**). After the number of attempts were unsuccessful or not efficient in terms of the conversion yield and reproducibility, due to the feasible migration of the exo-methylene to an internal olefin, it was found that the Beckmann rearrangement of the oxime (**20**),[10] prepared from the ketone (**18**) and hydroxylamine hydrochloride and pyridine, with thionyl chloride in tetrahydrofuran[11] at 0°C resulted in the formation of the lactam (**21**) as a single compound in 41% yield. Removal of the silyl group of **21** with aqueous hydrochloric acid, followed by treatment with methanesulphonyl chloride in dichloromethane gave the methanesulphonate (**22**) in 75% yield. An intramolecular alkylation of **22** with potassium carbonate in aqueous dioxane and subsequent desilylation of **23** with *p*-toluenesulphinic acid[9] in aqueous acetonitrile furnished the lactam (**24**), in 58% yield, whose spectroscopic data including the specific optical rotation $[\alpha]_D$- 95.0°(c=0.3, $CHCl_3$) {lit.,[2] $[\alpha]_D$ -98.3°(c=1.2, $CHCl_3$)} were identical with those reported.[2]

Since the lactam (**24**) has already been transformed into (-)-pumiliotoxin 251D (**1**),[2] this synthesis constitutes its formal synthesis and this synthetic route would be applicable to the chiral synthesis of other indolizidine alkaloids.

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8. Selected spectroscopic data for **13:** ν_{max}(CHCl3) 1730 and 1620 cm^{-1}; δ(CDCl3) 0.12(9H, s, SiMe3), 2.85-3.00(1H, m, CHCO), 4.89(1H, dt, *J* 4.9 and 4.9 Hz, CHOCO), 5.50(1H, dd, *J* 3.7 and 1.8 Hz, CH=C).
   For **14:** ν_{max}(CHCl3) 1730 and 1630 cm^{-1}; δ(CDCl3) 0.10(9H, s, SiMe3), 2.75-2.85(1H, m, CHCO), 4.85(1H, dt, *J* 4.9 and 1.8 Hz, CHOCO), 5.43(1H, dd, *J* 4.9 and 2.4 Hz, CH=C).
   For **18:** ν_{max}(CHCl3) 1750 and 1645 cm^{-1}; δ(CDCl3) 0.03(6H, s, Si*Me*2Bu), 0.11(9H, s, SiMe3), 0.87(9H, s, SiMe2*Bu*), 3.50-3.70(2H, m, CH_2OSi), 5.53(1H, dd, *J* 2.4 and 1.2 Hz, CH=C).
   For **21:** ν_{max}(CHCl3) 3400 and 1655 cm^{-1}; δ(CDCl3) 0.05 and 0.06(each 3H, each s, Si*Me*2Bu), 0.12(9H, s, SiMe3), 0.89(9H, s, SiMe2*Bu*), 3.55-3.75(2H, m, CH_2OSi), 4.03-4.13(1H, m, C*H*NH), 5.42(1H, s, CH=C), 6.57(1H, br s, NH).
   For **23:** ν_{max}(CHCl3) 1635 cm^{-1}; δ(CDCl3) 0.14(9H, s, SiMe3), 3.26(1H, dt, *J* 12.2 and 3.7 Hz, C*H*HNCO), 3.86(1H, dt, *J* 12.2 and 8.6 Hz, CH*H*NCO), 4.11(1H, dd, *J* 11.6 and 5.5 Hz, NCHC=), 5.49(1H, s, CH=C).
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