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# Stereocontrolled Synthesis of (±)-9,10-Dideoxynorribasine

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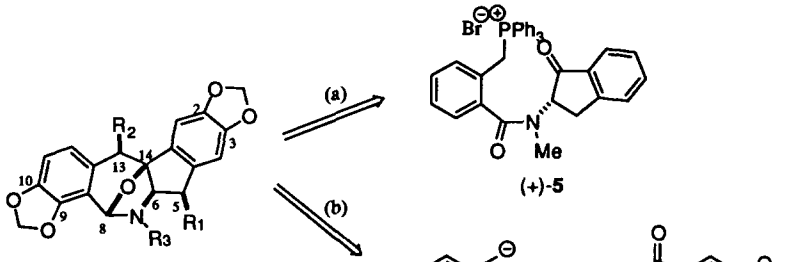
***Abstract.*** **(±)-9,10-Dideoxynorribasine was synthesized by a reaction sequence in which the key step was stereocontrolled formation of the C13-C14 bond by addition of *o*-cyanobenzyllithium to 2-(9-phenylfluoren-9-yl)-amino-1-indanone 6.** © 1997 Elsevier Science Ltd.

In 1983 we reported the isolation from *Fumariaceae* plants of (+)-ribasine (**1**)[1], the parent compound of a class of alkaloids that contain an 8,14-epoxy-indano[2,1-c][2]benzazepine in their skeleton and may be biogenetically related to the isoquinoline alkaloids[2]. Shortly afterwards, the hydroxyderivatives (+)-himalayamine **2**[3] and (+)-ribasidine **3**[4] were isolated and characterized, and, more recently, the *N*-demethyl analogue (+)-norribasine **4**[5] was described.




**1**, $R_1$=$R_2$=H, $R_3$=Me
**2**, $R_1$=OH, $R_2$=H, $R_3$=Me
**3**, $R_1$=H, $R_2$=OH, $R_3$=Me
**4**, $R_1$=$R_2$=$R_3$=H

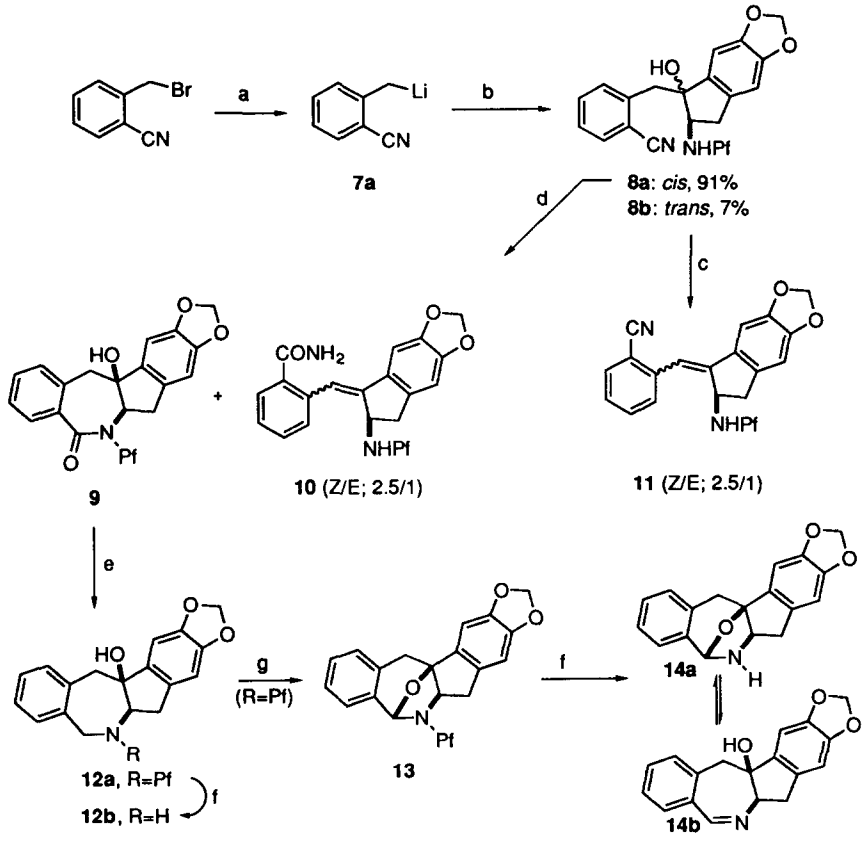
**Scheme 1**

The unprecedented indanobenzazepine structure of these alkaloids represents a challenging synthetic problem. Some time ago, we described an approach to the synthesis of (±)-2,3,9,10-tetradeoxyribasine in which the key step was formation of the C13-C14 double bond of the azepine ring by intramolecular Wittig reaction of the enantiomerically pure phosphonium salt **5** (Route a).[6] However, this strategy is unsuitable for the synthesis of the natural compounds because the basic conditions required for the Wittig reaction cause racemization at C-6 and subsequent hydroxylation at C-14 is non-stereoselective. We therefore sought alternative approaches to the synthesis of ribasine alkaloids.

In the work reported here we describe a stereocontrolled approach to indanobenzazepines that begins with formation of the C13-C14 bond by nucleophilic addition of an *ortho*-substituted benzylic anion **7** to the *N*-protected 2-amino-1-indanone **6**[7] (Route b). The *N*-protecting group chosen was the 9-phenylfluoren-9-yl

group (Pf) developed by Rapoport,[8] which should not only stabilize the labile α-aminoketone of **6**, thus avoiding self-condensation and enolization during the coupling reaction, but, by virtue of its steric bulk, should also direct the incoming nucleophile opposite to the α-amino group, allowing stereocontrolled generation of C14. Clearly, this nucleophile must contain an *ortho* substituent (G in **7**) that is susceptible to subsequent formation of the azepine ring and the oxygen bridge, and the method used to generate the benzylic anion must be compatible with this substituent. In this regard, we came across Kambe and Sonoda's very mild method for the α-lithiation of α-bromo-*o*-toluonitrile by low temperature lithium-tellurium exchange of its benzylic telluride (prepared *in situ* by reaction with lithium *n*-butyltellurorate).[9] So, we decided to test Route b using this lithiation method and thus the derived *o*-substituted benzylic anion as the synthetic equivalent of **7**.

The required benzylic anion **7a** was generated *in situ* by adding *n*BuLi at -105°C to a THF solution of the benzylic telluride prepared from the corresponding α-bromo-*o*-toluonitrile and *n*BuTeLi. Aminoindanone **6** was added to this cooled solution which was stirred for 15 min and allowed to warm to room temperature




a) i: *n*BuTeLi, THF, 0°C, 30 min; ii: *n*BuLi, -105°C, 5 min; b) **6**, THF, -105°C, 15 min; c) $H_2SO_4$, DME/$H_2O$, reflux, 7h; d) KOH, EtOH, rt, 20 h; e) i: $BH_3$·$SMe_2$, THF, reflux, 24 h; ii: TMEDA, 1:1 $CH_2Cl_2$/ether , rt, 10h; f) $CF_3CO_2H$, $CH_2Cl_2$, 0°C, 20 h; g) Fremy's salt, Py/$Na_2CO_3$, rt, 3 days

**Scheme 2**

before being quenched. Work-up afforded the desired *cis*-2-amino-1-indanol **8a** in 25% yield, a small amount of lactam **9** (15%) and, as the major product, benzamide **10** in 55% yield.[10] By contrast, when the reaction was quenched at low temperature and then worked up, the desired *cis*-2-amino-1-indanol **8a**[11] was isolated in an excellent 91% yield, together with 7% of the *trans* -2-amino-1-indanol **8b**.

The key intermediate **8a** afforded by this high-yielding, stereoselective coupling already has all the functionalities needed to form the benzazepine ring. We reasoned that the aldehyde resulting from reduction of nitrile **8a** would be trapped by the 1,2-aminoalcohol functionality, directly affording the desired epoxybenzazepine **13**. However, attempts at this approach using some of the available methods[12] led either to no reaction or to over-reduction to the primary amine. Next, we tried hydrolysis of the nitrile: under a variety of acidic conditions[13] hydrolysis failed to occur and only the elimination product **11** was isolated;[14] however under basic conditions, hydrolysis was accompanied by the desired intramolecular *N*-acylation, giving lactam **9** in 62% yield, and by some elimination to benzamide **10** (25%). The formation of this primary amide suggests that the elimination reaction is not just a simple dehydration *via* stilbene **11**, but rather the result of neighbouring group participation by the tertiary hydroxyl during hydrolysis of the nitrile, followed by β-elimination. Gratifyingly, alternative participation by the protected amino group predominated, giving the desired 2-benzazepinone **9** as the major product.

Final transformation of hydroxybenzazepinone **9** into indanobenzazepine **14** was accomplished as follows. Lactam **9** was reduced with $BH_3{\cdot}SMe_2$[15], and the resulting borane complex was destroyed using TMEDA-ether, thus affording aminoindanol **12a** in 85% yield. Attempts to remove the *N*-protecting group of **12a** by catalytic hydrogenation using either $Pd(OH)_2$ or Pd-C[16] as catalysts or under standard acidic conditions (TFA, $CH_2Cl_2$, rt)[17] gave complex mixtures. Only when **12a** was treated with TFA/$CH_2Cl_2$ at low temperature was the dihydronorribasine derivative **12b** obtained; however since it proved unstable on attempted chromatography, we decided to continue the synthesis using the protected derivative **12a**. Thus, **12a** was oxidatively cyclized[4] with Fremy's salt to the indanobenzazepine **13** in quantitative yield.[18] Finally removal of Pf under acidic conditions at low temperature gave (±)-9,10-dideoxynorribasine **14a**, which was isolated as an equilibrium mixture with **14b** (demonstrated by low temperature NMR spectroscopy). It is noteworthy that natural norribasine (**4**) does not show this equilibrium, possibly because opening of the ether bridge is disfavoured due to steric strain between the imine hydrogen (H8) and the methylenedioxy substituent.

Work is in progress to extend this synthetic methodology to the preparation of the natural ribasine alkaloids.

**Acknowledgements**

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11. The assignement of *cis*-stereochemistry to the major product (**8a**) was confirmed by its transformation to the ether-bridged derivative **13**; this type of cyclization would not have been possible for *trans*-**8b**.
**8a**: IR (film): ν= 2224 $cm^{-1}$ (CN). $^1$HNMR ($CDCl_3$, 250MHz): δ= 2.28 (dd, *J*=14.9, 7.6 Hz, 1H), 2.42 (dd, *J*=14.9, 9.8 Hz, 1H), 2.47 (br s, NH), 2.83 (dd, *J*=9.8, 7.6 Hz, 1H), 3.01 (d, *J*=13.6 Hz, 1H), 3.64 (d, *J*=13.6 Hz, 1H), 5.50 (s, 1H), 5.70 (d, J=1.2 Hz, 1H), 5.78 (d, J=1.2 Hz, 1H), 6.4 (s, 1H), 7.21-7.72 (m, 17H). $^{13}$CNMR ($CDCl_3$, 62.5 MHz): δ=37.87 ($CH_2$), 39.41 ($CH_2$), 67.15 (CH), 73.04 (C), 83.77 (C), 100.56 ($CH_2$), 104.82 (CH), 105.01 (CH), 114.64 (C), 118.13 (CN), 120.17 (CH), 120.45 (CH), 124.89 (CH), 124.98 (CH), 126.19 (2xCH), 126.67 (CH), 127.40 (CH), 128.03 (CH), 128.36 (CH), 128.43 (2xCH), 128.73 (CH), 128.51 (CH), 131.45 (CH), 131.62 (CH), 131.99 (CH), 132.22 (C), 136.47 (C), 140.34 (C), 140.82 (C), 141.44 (C), 144.84 (C), 145.82 (C), 147.46 (C), 150.11 (C), 150.52 (C).
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18. Indanobenzazepine **13**: $^1$HNMR ($CDCl_3$, 250MHz): δ= 1.75 (dd, *J*=15.0, 6.8 Hz, 1H), 2.50 (dd, *J*=15.0, 9.1 Hz, 1H), 2.73 (d, *J*=16.5, 1H), 2.86 (m, 1H), 3.65 (d, *J*=16.5 Hz, 1H), 5.69 (d, J=1 Hz, 1H), 5.71 (d, J=1 Hz, 1H), 6.07 (s, 1H), 6.34 (s, 1H), 7.13-7.48 (m, 15H), 7.67 (d, *J*=7.4 Hz, 1H), 7.74 (d, *J*=7.4 Hz, 1H), 8.29 (s, 1H). $^{13}$CNMR ($CDCl_3$, 62.5 MHz): δ=32.5 ($CH_2$), 38.58 ($CH_2$), 63.68 (CH), 70.01 (C), 72.40 (C), 100.61 ($CH_2$), 103.04 (CH), 105.50 (CH), 119.99 (CH), 125.36 (CH), 125.45 (CH), 126.27 (CH), 126.98 (CH), 127.08 (CH), 127.58 (CH), 127.81 (CH) 127.90 (CH), 128.13 (CH), 128.32 (CH), 128.64 (C), 131.67 (CH), 134.77 (C), 136.13 (C), 138.25 (C), 140.08 (C), 140.71 (C), 145.65 (C), 145.94 (C), 147.56 (C), 149.56 (C), 152.46 (C), 158.34 (CH).


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