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The First Total Synthesis of (±)-Ribasine

Lourdes Ollero, Luis Castedo and Domingo Domínguez*

Departamento de Química Orgánica, Facultade de Química, Universidade de Santiago y Unidad Asociada al CSIC.
15706 Santiago de Compostela, SPAIN.

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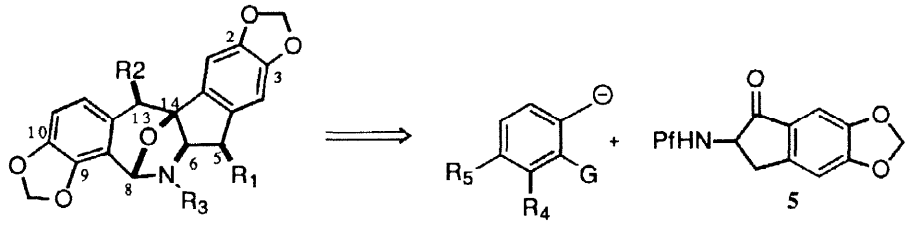
Abstract. The first total synthesis of (±)-ribasine was achieved by stereocontrolled addition of 3,4-methylenedioxy-substituted α-lithium-*o*-toluate **13c** to 2-(9-phenylfluoren-9-yl)-amino-1-indanone **5**.

Ribasine (**1**)[1], which was first isolated from *Fumariaceae* plants in 1983, is the parent compound of a class of alkaloids with an 8,14-epoxy-indano[2,1-c][2]benzazepine in their skeleton. Other members of this class are the hydroxy ribasines himalayamine (**2**)[2] and ribasidine (**3**)[3], and the *N*-demethyl congener norribasine (**4**)[4].



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

6a, R_4=R_5=H, G=CN
6b, R_4+R_5=OCH_2O, G=CN

Scheme 1

Challenged by the unprecedented indanobenzazepine structure of these alkaloids we began work on their synthesis. Following the strategy outlined in Scheme 1, we recently described the synthesis of (±)-9,10-dideoxynorribasine[5] by stereocontrolled addition of *o*-cyanobenzyllithium **6a** to the protected 2-amino-1-indanone **5**.[6] In this communication we report extension of this approach to the synthesis of racemic ribasine.

For generation of the methylenedioxy-substituted α-lithio-*o*-tolunitrile **6b**, we chose Kambe and Sonoda's method for the α-lithiation of α-bromo-*o*-toluonitrile.[7] The required precursor, **9a**, was straightforwardly prepared in 48% overall yield from 6,7-methylenedioxyphthalide **7**[8], by opening of the lactone ring with aqueous ammonia and hydrogenolysis of the resulting benzylic alcohol to *o*-toluamide **8**, followed by dehydration of the primary amide of **8** and bromination of the methyl group with NBS (Scheme 2).[9]

To generate lithiate **6b**, bromide **9a** was firstly converted to benzylic telluride **9b** by treatment with lithium *n*-butyltellurolate in THF. This then underwent fast lithium-tellurium exchange at low temperature, affording a dark red solution of **6b**. Aminoindanone **5** was added directly to this cold solution, and the reaction

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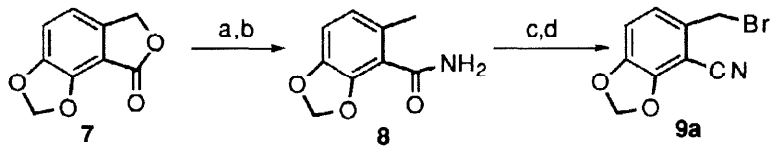
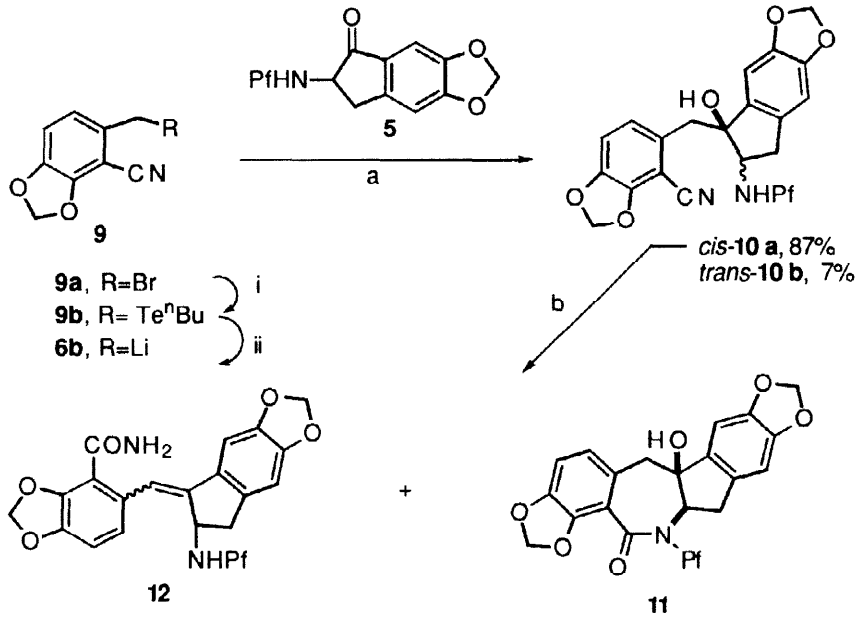


a) NH_3 aq./EtOH, reflux, 15h, 60%; b) H_2, Pd-C, MeOH, 2atm, 24h, 79%
c) $(CF_3CO)_2O$, Et_3N/THF, rt, 2h, 100%; d) NBS, CCl_4, hv, reflux,1.5 h, 100%

Scheme 2

was left for 15 minutes and then quenched at low temperature. After work up, chromatography afforded the desired coupling product *cis*-**10a** in 87% yield, together with 7% yield of the *trans*-2-amino-1-indanol **10b**. Unfortunately, basic hydrolysis of the nitrile of **10a** gave only a 20% yield of the desired 2-benzazepinone **11**[10], the major product being the stilbenic benzamide **12** (60% yield). This result is somewhat surprising given that the benzazepinone was the major product in the synthesis of (±)-9,10-dideoxynorribasine.



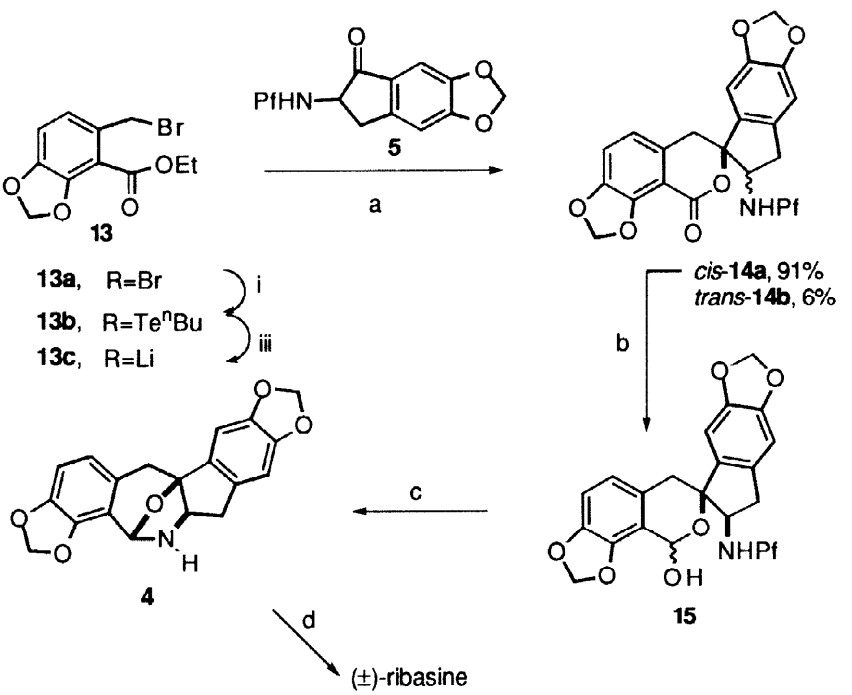
a) i: *n*BuTeLi, THF, 0°C, 30 min; ii: *n*BuLi, -105°C, 5 min; iii: **5**, THF, -105°C, 15 min;
b) KOH, EtOH, rt, 2h

Scheme 3

Because of the low yield of lactam **11** and the difficulty involved in its isolation, we sought an alternative approach to ribasine using our basic strategy (Scheme 1), but changing group G in **6** for a group more easily hydrolysed than nitrile, so as to avoid formation of the undesired β-elimination product. An ester group fulfils this requirement and is also chemically compatible with Kambe and Sonoda's method for generation of the benzylic anion. Moreover, as we have already reported,[11] when G is an ester group it can undergo intramolecular cyclization with the hydroxyl at the coupling stage, without β-elimination, affording a lactone which would be afterwards susceptible of formation of the azepine ring.

3,4-methylenedioxy-substituted α-bromo-*o*-toluate **13a**[11] was chosen as the precursor of the ester equivalent of **6b** (G=CO_2Et). Gratifyingly, treatment of a mixture of benzylic telluride **13b** (prepared *in situ* by reaction of **13a** with *n*-butanetellurolate) and aminoindanone **5** with *n*-BuLi afforded an excellent 91% yield of

the dihydroisocoumarin with the desired *cis*-stereochemistry (**14a**)[12], and only a 6% yield of the unwanted *trans*-isomer **14b**. Next, lactone **14a** was tranformed in only two steps into (±)-norribasine. First, reduction with DIBAL-H, which gave an anomeric mixture of lactol **15**; and then acidic hydrolysis of the *N*-Pf group at low temperature, allowing the primary amine to condense *in situ* with the neighbouring lactol (80% overall yield). The (±)-norribasine obtained had ^{1}H-NMR and mass spectra identical to the natural alkaloid.[4] Finally norribasine was transformed into ribasine by reductive methylation. In our hands, use of the published method[13] gave a 1:1 mixture of ribasine and dihydrorribasine[3], the later resulting from reductive opening of the ether bridge. By contrast, treatment with formaldehyde for one hour at reflux followed by reduction with $NaBH_4$ for four hours at room temperature, afforded (±)-ribasine exclusively. This synthetic compound had identical tlc, ^{1}H-NMR and MS to an authentic example of natural (+)-ribasine. Work is in progress to prepare the enantiomerically pure alkaloid.



a) i: *n*BuTeLi, THF, 0°C, 30 min; ii: **5**, -105°C; iii: *n*BuLi, -105°C, 15 min;
b) DIBAL-H, THF, -78°C, 2h; c) TFA, CH_2Cl_2, 0°C, 5h; d) i: CH_2O, MeOH, reflux, 60 min.; ii: $NaBH_4$, MeOH, rt, 4h.

Scheme 4

Acknowledgements

We thank the Dirección General de Enseñanza Superior (Project PB95-0824) and the Xunta de Galicia (Project XUGA20907-B96) for financial support. L. Ollero thanks the Xunta de Galicia for a predoctoral fellowship.

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7. Kanda, T.; Kato, S.; Sugino, T.; Kambe, N.; Ogawa, A.; Sonoda, N. *Synthesis* **1995**, 1102.
8. Sinnababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 2356.
9. All new compounds were fully characterized spectroscopically and had satisfactory elemental analyses or molecular weights by high-resolution mass spectra.
10. Benzazepinone **11**: ^{1}HNMR ($CDCl_3$, 250MHz): δ= 2.13 (dd, *J*=13.3, 6.8 Hz, 1H), 2.22 (m, 1H), 2.76 (d, *J*=15.6 Hz, 1H), 2.85 (m, 1H), 3.04 (d, *J*=15.6 Hz, 1H), 5.83 (d, *J*=1Hz, 1H), 5.86 (d, *J*=1Hz, 1H), 6.20 (s, 2H), 6.35 (s, 1H), 6.40 (s, 1H), 6.49 (s, 1H), 6.56 (d, *J*=7.7Hz, 1H), 6.88 (d, *J*=7.7 Hz, 1H), 6.97 (d, *J*=7.4 Hz, 1H), 7.10-7.45 (m, 9H), 7.61 (d, *J*=7.5Hz, 1H), 7.70 (d, *J*=7.5 Hz, 1H). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ=38.18 (CH_2), 38.61(CH_2), 63.02 (CH), 66.32 (C), 72.73 (C), 101.09 (CH_2), 102.46 (CH_2), 103.82 (CH), 105.47 (CH), 111.10 (CH), 112.52 (C), 119.85 (CH), 120.07 (CH), 120.12 (CH), 125.22 (CH), 125.68 (CH), 126.12 (CH), 127.23 (CH), 127.84 (CH), 127.89 (CH), 128.18 (CH), 128.26 (CH), 128.49 (CH), 130.40 (C), 133.21 (C), 136.42 (C), 139.92 (C), 140.63 (C), 144.44 (C), 146.87 (C), 147.81 (C), 147.96 (C), 148.24 (C), 148.60 (C), 150.93 (C), 163.72 (CO).
11. Ollero, L.; Castedo. L.; Domínguez, D. *Synlett* **1997**, 1047.
12. Dihydroisocoumarin **14a**: ^{1}HNMR ($CDCl_3$, 250MHz): δ= 1.89 (d, *J*=9.3 Hz, 1H), 2.03 (dd, *J*=15.4, 7.6 Hz, 1H), 2.18 (dd, *J*=15.4, 6.9 Hz, 1H), 3.18 (d, *J*=16.5 Hz, 1H), 3.24 (m, 1H), 3.49 (d, *J*=16.5 Hz, 1H), 5.82 (s, 2H), 6.20 (d, *J*=1Hz, 1H), 6.23 (d, *J*=1Hz, 1H), 6.35 (s, 1H), 6.49 (s, 1H), 6.81 (d, *J*=8.1Hz, 1H), 6.97-7.72 (m, 14H). ^{13}CNMR ($CDCl_3$, 62.5 MHz): δ=32.72 (CH_2), 37.79 (CH_2), 64.35 (CH), 72.79 (C), 92.57 (C), 101.07 (CH_2), 102.88 (CH_2), 103.96 (CH), 105.24 (CH), 109.34 (C), 112.75 (CH), 119.67 (CH), 120.02 (CH), 120.26 (CH), 124.76 (CH), 125.50 (CH), 125.94 (CH), 127.22 (CH), 127.67 (CH), 128.13 (CH), 128.46 (CH), 128.61 (CH), 131.18 (C), 133.10 (C), 135.16 (C), 139.69 (C), 141.03 (C), 145.11 (C), 146.80 (C), 148.22 (C), 148.50 (C), 149.39 (C), 151.02 (C), 162.00 (CO).
13 In ref. 4, methylation was carried out by refluxing **4** with CH_2O in MeOH followed by treatment with sodium borohydride at reflux for one hour.