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A new synthesis of (−)-debromoflustramine B, (+)-*ent*-debromoflustramine B and (+)-debromoflustramide B

A. Sofia Cardoso, Natarajan Srinivasan, Ana M. Lobo* and Sundaresan Prabhakar*

Secção de Química Orgânica Aplicada, Departamento de Química, Centro de Química Fina e Biotecnologia and SINTOR-UNINOVA, campus Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, 2829 Monte de Caparica, Portugal

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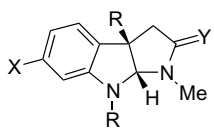
Abstract—The first synthesis of (−)-debromoflustramine B is reported. Appropriate structural modifications of an optically pure Barton ester, obtained in five steps from *N*-acetyl-L-tryptophan methyl ester, lead to the alkaloid.

Debromoflustramine B[1] (**1**) incorporating the hexahydropyrrolo[2,3-*b*]indole skeleton and other structurally related alkaloids, such as flustramines A (**2**) and B (**3**) have been isolated from *Flustra foliacea*.[2]

Whilst various syntheses for racemic debromoflustramine B[3] as well as one for its (+)-*ent*-isomer[4] are reported, there is no synthesis available to-date for the natural product. We report herein the first such synthesis.

The requisite starting material (−)-1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxylate (**5**) (Scheme 1) [enantiomerically pure, as determined by ^{1}H NMR with the shift reagent, Eu(tfc)$_3$], was obtained from *N*-acetyl-L-tryptophan methyl ester (**6**) using the procedure of Witkop.[5] Under conditions generally considered to favour *N*-alkylation[6] the indole **5** underwent predominantly *C*-allylation (NaH, dimethylallyl bromide, DMF) to provide a diastereoisomeric mixture of prenylated compounds **7** and **8**[7] (60%) and the *N*-allyl isomer **9** (11%). The *N*-allyl pyrrole **9** was readily removed from its isomers by chromatography and the separation of the diastereoisomers **7** and **8** (0.9:1 ratio) was deferred to a later stage[8] in the synthesis. The mixture was reduced and the resulting secondary amines **10** and

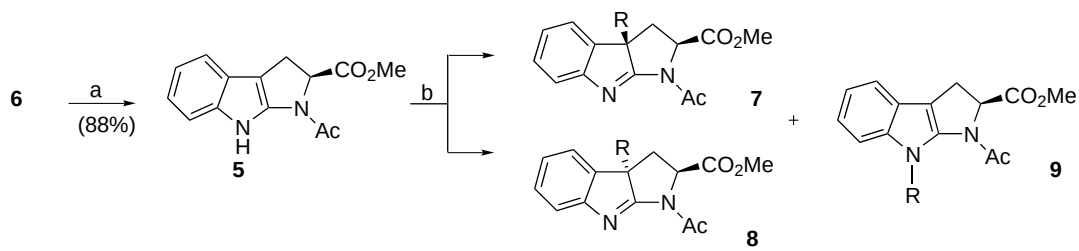


1 R = $CH_2CH{=}CMe_2$; X = H ; Y = H,H
(-)-debromoflustramine B

2 R = $CMe_2CH{=}CH_2$; X = Br ; Y = H,H
(-)-flustramine A

3 R = $CH_2CH{=}CMe_2$; X = Br ; Y = H,H
(-)-flustramine B

4 R = $CH_2CH{=}CMe_2$; X = Br ; Y = O
(-)-flustramide B



Scheme 1.

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* Corresponding authors. Tel.: +351-21-2948387; fax: +351-21-2948550; e-mail: aml@mail.fct.unl.pt; sp@dq.fct.unl.pt

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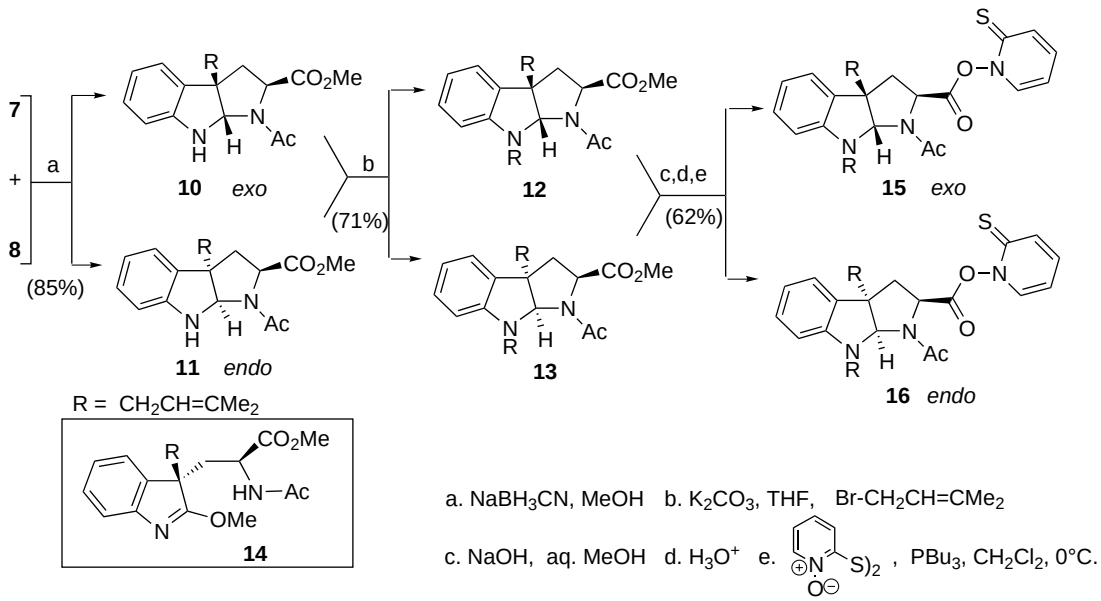
11 (0.7:1.0 ratio) converted into the *C*,*N*-diallyl esters **12** and **13** (1:2 ratio) (Scheme 2). This unfortunate progressive reduction in the diastereoisomeric mixture ratio in favour of the *undesired* isomer was due to the greater intrinsic instability of the *exo* isomers vis à vis the corresponding *endo* isomers,[9] both during their reactions and work-up. This was reflected in the isolation of the ring-opened product **14** resulting only from the *exo* isomer **7** during the reduction.[10]

Saponification of **12** and **13**, followed by acidification of the mixture, provided the corresponding acids from which the requisite Barton esters[11] **15** and **16** (1:2 ratio) were readily secured. Although sensitive to heat and light, they could nevertheless be separated efficiently by column chromatography into pure *exo* **15** and *endo* **16** isomers. Exposure of an ethereal solution of **15** to $Sb(SPh)_3$ and air[12] furnished the hydroxy-amide **17** (Scheme 3). Similarly **16** yielded **18**. All attempts to impart hydrolytic instability to the *N*-acetyl group by oxidation of the adjacent OH group of either **17** or **18** (Swern; Dess–Martin periodinane; Pt/O_2) to the carbonyl compound failed.

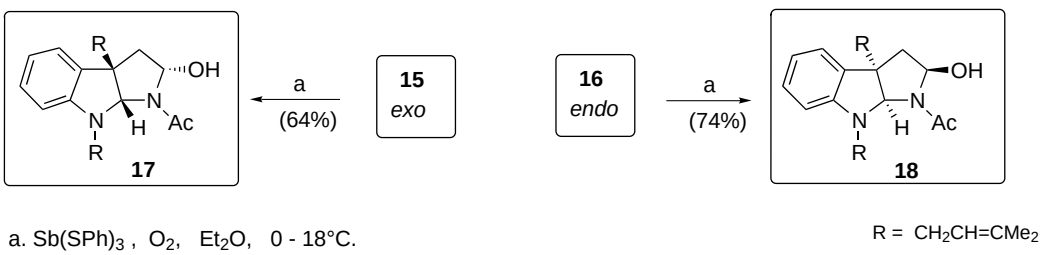
However, the *N*-deacetylation of the enamide **19** (Scheme 4) obtained by heating a xylene solution of **17**, to the imine **20**, could be accomplished with a methanolic methoxide solution containing hydrazine. LAH reduction of **20** yielded the secondary amine **21**. Although the conversion of the latter in its racemic form to the (±)-alkaloid is reported[3a] to occur with $NaCNBH_3/H_2C{=}O$ in 57% yield, the amine **21** however did not yield the desired product. An 18% yield (46% based on recovered starting material) of (–)-debromoflustramine B (**1**) $[\alpha]_D^{25} = -97.5$ ($c = 0.06$, $CHCl_3$), lit[1] $[\alpha]_D^{20} = -98.2$ ($c = 0.02$, $CHCl_3$)], possessing NMR spectra (^1H; ^{13}C) identical with those reported for the natural product, was however obtained on methylation of the same with MeI.

Similarly **18**, furnished (+)-*ent*-debromoflustramine B [(+)-*ent*-**1**] $[\alpha]_D^{20} = +96.4$ ($c = 0.06$, $CHCl_3$).

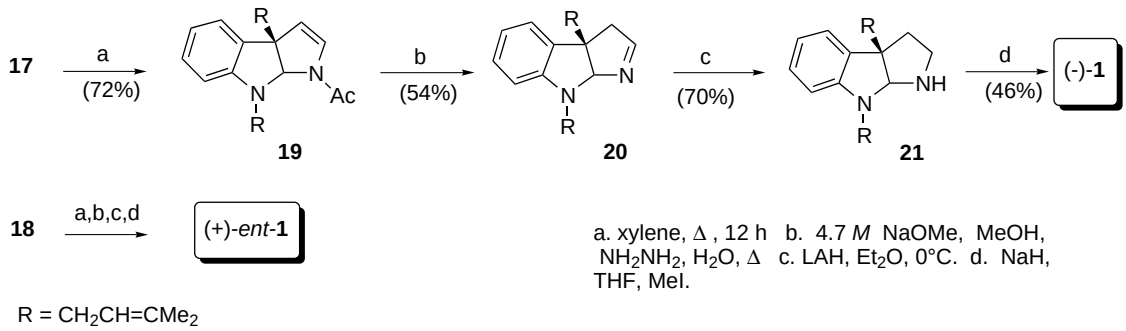
The Barton ester **16**[13] (Scheme 5) on treatment with KOBu-*tert*-BuOH in THF saturated with dried air (P_2O_5) led after acidification of the mixture, to the carboxylic acid **22** (40%), thiopyridone **23** (18%), 1,3-bis-dimethylallylindole **24** (30%) and the pyrrolidone **25a** (15%). The latter on methylation furnished (+)-debromoflustramide B (**25b**) [92%; $[\alpha]_D^{25} = 36$ ($c = 0.03$, CH_2Cl_2)], the ^1H and ^{13}C spectra of which were identical with those reported for the racemic substance.[3c,3e]



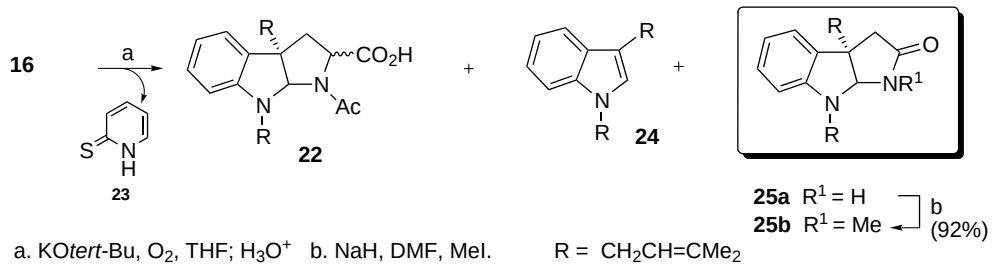
Scheme 2.



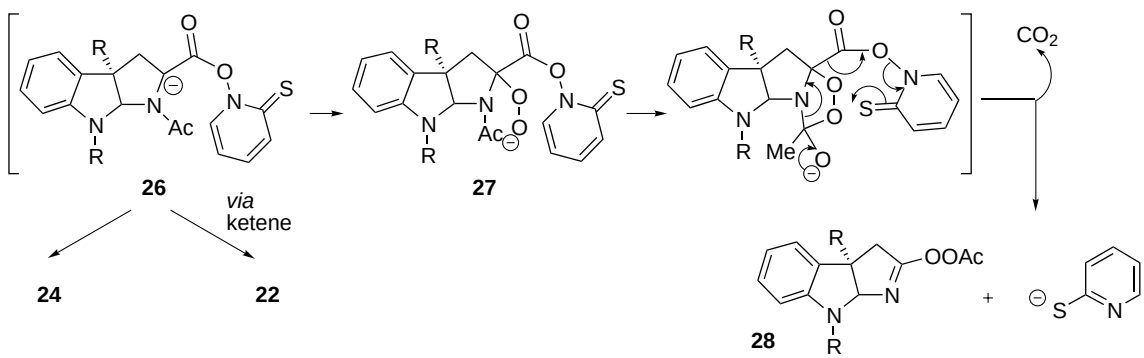
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

A possible mechanism for the formation of these products is outlined below (Scheme 6). Thus, whilst the unimolecular fragmentation of the carbanion **26** accounts for **22** and **24**, its reaction with O_2 could generate the hydroperoxide anion **27** from which the imino peracetate **28** and pyridine-2-thiolate are formed. An oxidation–reduction reaction between the latter two species would lead to **25a**.

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7. Other alkylations methods involving chiral quaternary salts of Cinchona alkaloids (see: Dolling, U. H.; Davis, P.; Grabowski, C. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447) or Adogen 464 furnished **7** and **8** (60%) in 1:2 ratio. All new compounds gave satisfactory microanalyses or high resolution mass spectra and spectral data.
8. All diastereoisomers could be separated into pure compounds on a small scale at each step of the synthesis, but with significant loss in yields.
9. Torsional factors or favourable secondary orbital interactions between the aromatic ring and the ester group have been invoked as a possible reason for the enhanced stability of the *endo* isomers vis à vis the *exo* isomers, see: Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin 1* **1991**, 1693–1699.
10. The isolation of **14** would imply that the bicyclic imine **7**, possibly due to steric strain, undergoes a faster reduction with $NaCNBH_3$ relative to **14**, also an imine, under the experimental conditions employed.
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13. The choice of **16** was dictated solely by its ready availability vis à vis **15**.