Synthesis of Diversely Functionalised Dibenzylbutyrolactones and Aryltetralins from Silylated Cyanohydrin Anions

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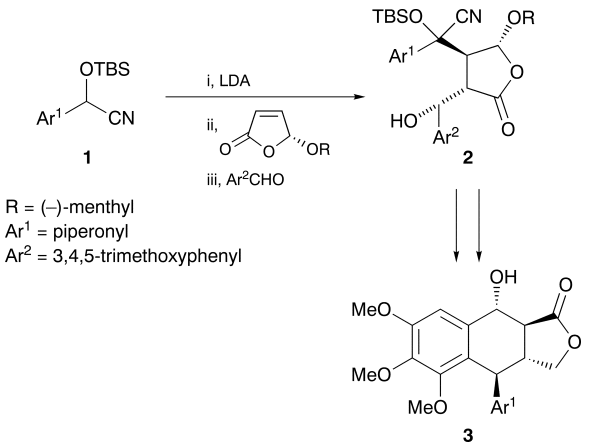
The aryltetralins **7a** and **7b** and the keto-lactone **8** are synthesised by cyclisation and deprotection of the conjugate addition products **4a** and **4b**; the structure of **7b** was unambiguously confirmed by an X-ray structural analysis.

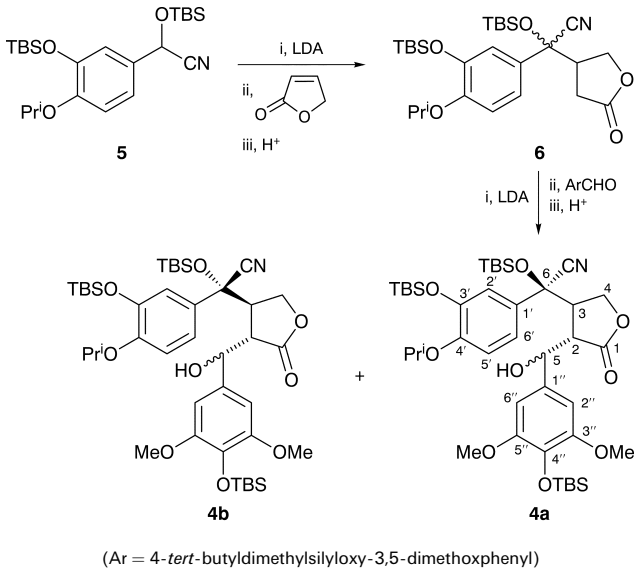
Following the methodology developed by Iwasaki *et al.*[1–3] we have shown that tandem conjugate addition by anions derived from *tert*-butyldimethylsilylcyanohydrins **1** to butenolides proceeds stereoselectively to give dibenzylbutrolactones **2**, which in turn afford access to aryltetralin lignans **3** (Scheme 1).[4] In order to synthesise differentially protected lignans belonging to the dibenzylbutyrolactone and aryltetralin series we have now prepared the tandem conjugate addition product **4** and have examined its reactions with trifluoroacetic acid (TFA) and tetrabutylammonium fluoride (TBAF). The compounds produced are potential precursors for the biotechnological production of clinically important podophyllotoxin derivatives, and for investigation of the stereochemistry of the biosynthetic pathway.[5–7]

The *tert*-butyldimethylsilylcyanohydrin **5** was synthesised in 3 steps from 3,4-dihydroxybenzaldehyde. Treatment of **5** with LDA followed by butenolide gave the adduct **6** in 80% yield as a 4:1 mixture of two diastereoisomers (Scheme 2). Treatment of the mixture with LDA followed by 4-*tert*-butyldimethylsilyloxy-3,5-dimethoxybenzaldehyde gave two products **4a** (30%) and **4b** (59%) which could be separated by column chromatography. Both **4a** and **4b** consisted of a mixture of two epimers which differed in their configuration of the benzylic OH group.

Cyclisation of **4a** with TFA at 0 °C afforded a single product **7a** in 61% yield while cyclisation of **4b** under the same conditions gave the C-4 epimer **7b** in 58% yield, the structure of which was confirmed by X-ray crystallography (Fig. 1).



Scheme 1



(Ar = 4-*tert*-butyldimethylsilyloxy-3,5-dimethoxphenyl)

Scheme 2

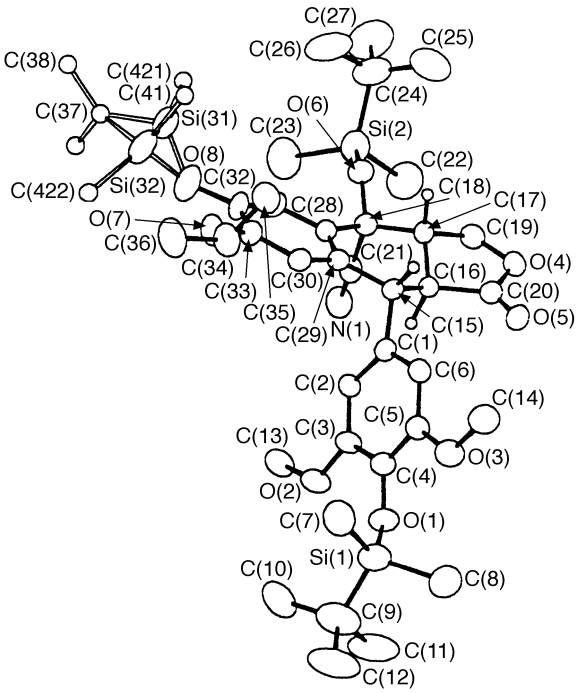


Fig. 1 X-Ray crystal structure of **7b**

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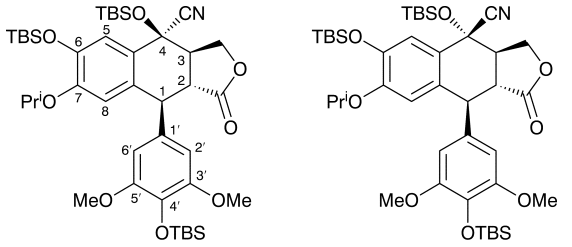

Scheme 7a and 7b

In a second series of experiments the tandem conjugate addition products **4a** and **4b** were treated with TBAF at 0 °C, with a view to regenerating the carbonyl group at C-6.In the event **4a** or **4b** gave the same fully desilylated compound **8** in 80–99% yield as a mixture of the two epimeric alcohols. In contrast, treatment of **4b** with TBAF at −78 °C gave a mixture of two partially deprotected compounds **9** and **10**, each as a mixture of epimeric alcohols. Further treatment of **9** with TBAF at 0 °C converted it into **8** (Scheme 3).

Crystal data for **7b**.—$C_{42}H_{67}NO_8Si_3$, $M_r = 798$, $F(000) = 864$, triclinic, $a = 7.183(4)$, $b = 17.383(3)$, $c = 19.708(3)$ Å, $V = 2409(2)$ Å^3, $\alpha = 81.52(1)$, $\beta = 83.34(4)$, $\gamma = 84.21(4)^\circ$, space group $P\bar{1}$, $Z = 2$, $D_x = 1.101$ mg m^{-3}, λ(Cu-Kα) = 1.54178 Å. The X-ray data were collected using an Enraf-Nonius CAD-4 X-ray diffractometer.

Techniques used: ^{1}H and ^{13}C NMR, MS, IR, X-ray crystallography

References: 13

Tables: 10 (^{1}H and ^{13}C NMR spectra of **4a**, **4b**, **6**, **7a** and **7b** and X-ray data for **7b**)

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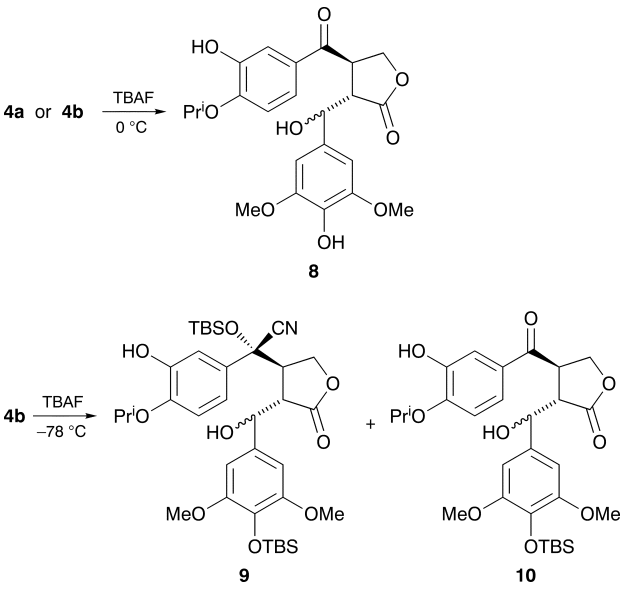

Scheme 3

References cited in this synopsis

1 T. Ogiku, S. Yoshida, M. Takahashi, T. Kuroda, H. Ohmizu and T. Iwasaki, *Tetrahedron Lett*., 1992, **33**, 4473, 4477.
2 T. Ogiku, S. Yoshida, T. Kuroda, M. Takahashi, H. Ohmizu and T. Iwasaki, *Bull. Chem. Soc. Jpn*, 1992, **65**, 3495.
3 Y. Moritani, C. Fukushima, T. Ogiku, T. Ukita, T. Miyagishima and T. Iwasaki, *Tetrahedron Lett*., 1993, **34**, 2787.
4 A. Pelter, R. S. Ward and N. P. Storer, *Tetrahedron*, 1994, **50**, 10829.
5 J. P. Kutney, M. Arimoto, G. M. Hewitt, T. C. Jarvis and K. Sakata, *Heterocycles*, 1991, **32**, 2305.
6 J. P. Kutney, Y. P. Chen, S. Gao, G. M. Hewitt, F. Furi-Brena, R. K. Milanova and N. M. Stoynov, *Heterocycles*, 1993, **36**, 13.
7 J. P. Kutney, X. Du, R. Naidu, N. M. Stoynov and M. Takemoto, *Heterocycles*, 1996, **42**, 479.