Asymmetric Synthesis of (3*S*)-2,3,4,5-Tetrahydropyridazine-3-carboxylic Acid

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The title compound **1a** is prepared by a two-step sequence from the cycloadduct **5d**, derived from di(*tert*-butyl) azodicarboxylate and the diene **4b** by a hetero Diels–Alder reaction.

Enantiopure non-proteinogenic amino acids are of considerable current interest.[1] As well as serving as precursors of atypical peptides and as building blocks in organic synthesis, such compounds and their derivatives may possess useful biological properties. The dehydropiperazic acid **1a** provides an example. It is a constituent of antrimycins—linear heptapeptides with antitubercular activity.[2] **1a** and its antipode are also present in L-365, 209, a cyclic hexapeptide which acts as an oxytocin antagonist.[3] Prompted by the recent communication of Nakamura and Shin[4] and Schmidt and Riedl[5] describing the synthesis of compound **1b** employing Evans' methodology, we now report on the asymmetric synthesis of compounds **1a** and **1b** featuring a highly diastereoselective hetero Diels–Alder reaction.

In earlier work, we showed that (*E*)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-dienes displayed a notable diastereofacial selectivity in their reactions with cyclic dienophiles under thermal conditions. For example, the diene **2** underwent reaction with *N*-phenylmaleimide in benzene to give an 86:14 mixture of the cycloadduct **3** and its diastereoisomer; compound **3** was isolated in 58% yield after crystallisation.[6] Based upon these findings, we decided to prepare the diene **4a** and to examine its reactions with azodicarboxylates in the hope of gaining access to cycloadducts of type **5** (R^2 = Me), potential precursors of targets of type **1**.

The propenal **6**[7,8] underwent a Wittig condensation (CH_2Cl_2, 20 °C) with the phosphorane **7a** to give a 4:1 mixture of the diene **4a** and its diastereoisomer. Following chromatography and crystallisation, the diene **4a**, m.p. 123–125 °C, $[\alpha]_D^{20}$ −24 (0.7% in CH_2Cl_2), was isolated in 54% yield.

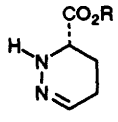
The diene **4a** reacted with diethyl azodicarboxylate (EtOAc, 70 °C, 3 days) to give the cycloadduct **5a** (82% yield after crystallisation), m.p. 135–136 °C, $[\alpha]_D^{20}$ −60 (0.46% in CH_2Cl_2) and with bis(2,2,2-trichloroethyl) azodicarboxylate (PhMe, 100 °C, 7 h) to afford the cycloadduct **5b** (60% yield after crystallisation), m.p. 152–153 °C, $[\alpha]_D^{20}$ −59 (0.73% in CH_2Cl_2). On the basis of their 300 MHz ^1H NMR spectra measured in deuteriochloroform at *ca.* 55 °C, both compounds were diastereomerically pure. To avoid the co-production of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose, it was necessary to conduct the reaction of **4a** with di(*tert*-butyl) azodicarboxylate at *ca.* 40 °C and to use an excess (*ca.* 3 mol equiv.) of the dienophile. Thus, when the reactants were heated in boiling dichloromethane for *ca.* 5 days and the product subjected to chromatographic purification, the cycloadduct **5c**, m.p. 88–90 °C, $[\alpha]_D^{20}$ −62 (0.3% in CH_2Cl_2), was isolated in 77% yield. 300 MHz ^1H NMR spectroscopy (CD_3SOCD_3; 100 °C) indicated that the material was a single diastereoisomer.

Hydrogenation (H_2, 10% Pd/C, EtOAc) of compound **5c** provided the piperazine **8a**, m.p. 96–98 °C, $[\alpha]_D^{20}$ −5 (0.22% in CH_2Cl_2), in 87% yield. In the presence of trifluoroacetic acid, the piperazine **8a** was transformed into a mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and compound **1b**, which was separated by silica gel chromatography; **1b**, $[\alpha]_D^{20}$ +125 (1.6% in MeOH) [lit.,[4] +139 (0.8% in MeOH)], was isolated as a syrup in 57% yield.

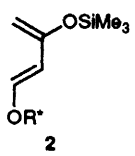
The enantiomeric purity of the ester **1b** was established by its conversion into the dinitrophenyl derivative **9a**, m.p. 94–95 °C (lit.,[4] 95–96 °C), $[\alpha]_D^{20}$ −294 (0.3% in $CHCl_3$) {lit.,[4] $[\alpha]_D^{23}$ −296.3 (0.3% in $CHCl_3$)} by sequential treatment with sodium cyanoborohydride in methanol and with 1-fluoro-2,4-dinitrobenzene in ethanol.

Since attempts to transform the ester **1b** into the acid **1a** were unsatisfactory, the synthesis of compound **5d** was undertaken. It was envisaged that **5d** would afford the dehydropiperazic acid **1a** by a hydrogenation–trifluoroacetolysis sequence.

The diene **4b**, m.p. 110–111 °C, $[\alpha]_D^{20}$ −18 (0.3% in CH_2Cl_2), obtained (56% yield after chromatography and crystallisation) from the reaction of the propenal **6** with the phosphorane **7b**, reacted with di(*tert*-butyl) azodicarboxylate (PhMe, *ca.* 85 °C, 5 days) to give the cycloadduct **5d** (76% yield after chromatography). Hydrogenation of **5d** and crystallisation of the product provided the acid **8b**, m.p. 100–101 °C, $[\alpha]_D^{20}$ −5 (0.38% in CH_2Cl_2), in 78% yield. When treated with trifluoroacetic acid, the acid **8b** was transformed



1a; R = H
b; R = Me



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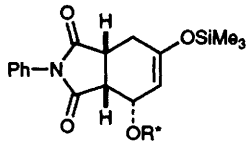

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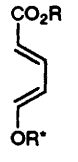
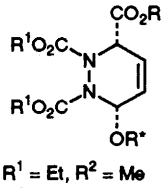
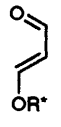


4a; R = Me
b; R = $PhCH_2$



5a; R^1 = Et, R^2 = Me
b; R^1 = Cl_3CCH_2, R^2 = Me
c; R^1 = Bu^t, R^2 = Me
d; R^1 = Bu^t, R^2 = $PhCH_2$



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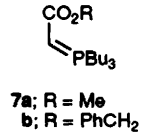
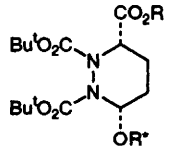
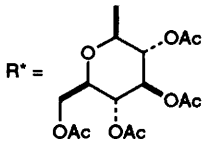


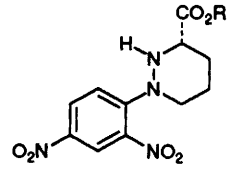
7a; R = Me
b; R = $PhCH_2$



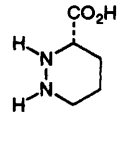
8a; R = Me
b; R = H



R* =



9a; R = Me
b; R = H



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into a mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and the dehydropiperazic acid **1a** which was separated by partition between dichloromethane and water; compound **1a**, as its trifluoroacetic acid salt, $[\alpha]_D^{20}$ +62 (0.3% in MeOH), was isolated from the aqueous phase as an oil in 98% yield.

The enantiomeric purity of the acid **1a** was established by its conversion into the dinitrophenyl derivative **9b**, m.p. 150–151 °C (lit. for the enantiomer *ent*-**9b**, 151.5–152[9] and 150.5–151.5 °C[10]), $[\alpha]_D^{20}$ −321 (0.5% in MeOH) [lit. for the enantiomer *ent*-**9b**, +324.6 (1% in MeOH)[9] and +341 (1% in MeOH)[10]] by sequential treatment with sodium cyanoborohydride and 1-fluoro-2,4-dinitrobenzene. Furthermore, treatment of the acid **9b** with diazomethane provided the ester **9a**, m.p. 96–97 °C, $[\alpha]_D^{20}$ −289 (0.8% in $CHCl_3$).

These findings are of interest in several respects. First, although the reaction of dienes with azo dienophiles has been extensively studied,[11] the results provide the first examples involving dienes bearing a detachable stereodirector. Secondly, the high diastereoselectivity displayed in the hetero Diels–Alder reaction is notable considering that acyclic dienophiles are involved (earlier, we found[8] that the diastereofacial reactivity of the diene **2** was poorer towards tetracycanoethylene than towards *N*-phenylmaleimide). Thirdly, it is worth pointing out that the absolute stereochemical outcome of the cycloaddition reactions is in accord with expectations based upon our previously proposed model.[8,12] Finally, it should be noted that the array of functionality present in cycloadducts of type **5** offers opportunities for extensive synthetic manipulations.

Recently, Hale *et al.*[10] have described an asymmetric synthesis of the piperazic acid **10** and its antipode *ent*-**10** using Evans' methodology.

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