Diastereoselective Conjugate Addition of Ammonia in the Synthesis of Chiral Pyrrolidines

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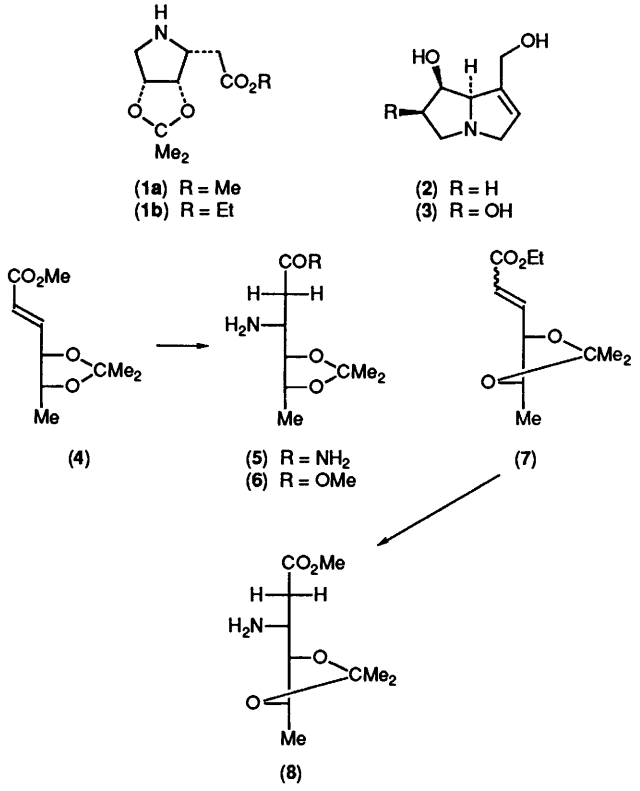
threo-Selectivity in the conjugate addition of ammonia to 4,5-isopropylidenedioxypent-2-enoic esters has been exploited in a new synthesis of homochiral pyrrolidines; the origin of the diastereoselectivity is discussed.

The pyrrolidine esters (**1a,b**)[1,2] are important intermediates in the synthesis of the necine bases retronecine (**2**) and crotanecine (**3**) from D-ribose[1] and D-erythrose.[1,2] We have now explored a further route to the esters which depends on diastereoselective conjugate addition of ammonia to an α,β-unsaturated ester under the influence of a neighbouring isopropylidenedioxy group.

It was shown by Dyong and Bendlin[3] that reaction of the (racemic) α,β-unsaturated ester (**4**) with methanolic ammonia at 100 °C gives mainly the DL-*arabino* amine (**5**); at room temperature the amino ester (**6**) is formed.[4] Fuganti and his co-workers found that addition of ammonia, in methanol at 0 °C to the L-*threo* ester (**7**), in either *Z* or *E* configuration, affords the amine (**8**) with L-*xylo* configuration as the major product,[5] and other cases have been described.[6] In all of these examples the new chiral centre generated by the introduction of the amino group has a *threo* relationship to the vicinal oxygenated centre, independent of the stereochemistry of the alkene (*Z,E*) and of the cyclic acetal group (*erythro*, *threo*). Similar results have been obtained using benzylamine.[7]

From the parent alcohols (**9**) and (**11**)[2] we have prepared the methanesulphonates (**10**) and (**12**) and studied their reactions with saturated ethanolic ammonia at room temperature. The sulphonates (**10**) and (**12**) each have two sites of potential reactivity towards nucleophiles. We were confident that conjugate addition would take place as the first step, followed by intramolecular displacement as the cyclization step, rather than intermolecular attack at C-6 by ammonia. The latter reaction has been shown to require forcing conditions in similar substrates.[8,9] After 114 h the *Z*-alkene (**10**) gave, as sole detectable product, the pyrrolidine (**1b**),[2] isolated in 88% yield after chromatography on silica doped with triethylamine; the D-*arabino* amine (**13**) is, presumably, an intermediate. Under identical conditions the *E*-alkene (**12**) reacted cleanly with ammonia in 96 h to give a mixture of pyrrolidines (**1b**)[2] and (**15**)[2] (81%; 9:1 ratio) purified by chromatography to give (**1b**) (70%) and (**15**) (8%). The pyrrolidines were not interconverted under the reaction conditions; the D-*ribo* amine (**14**) is probably a precursor of (**15**). As a further example of *threo*-diastereoselectivity in the conjugate addition the methanesulphonate (**17**) of the alcohol (**16**)[10] was treated with saturated ethanolic ammonia for 103 h to give, after chromatography, an inseparable mixture of pyrrolidines (**18**) and (**19**) (80%; 9:1 ratio), $[\alpha]_D$ 0° (*c* 0.9 in CH_2Cl_2).†

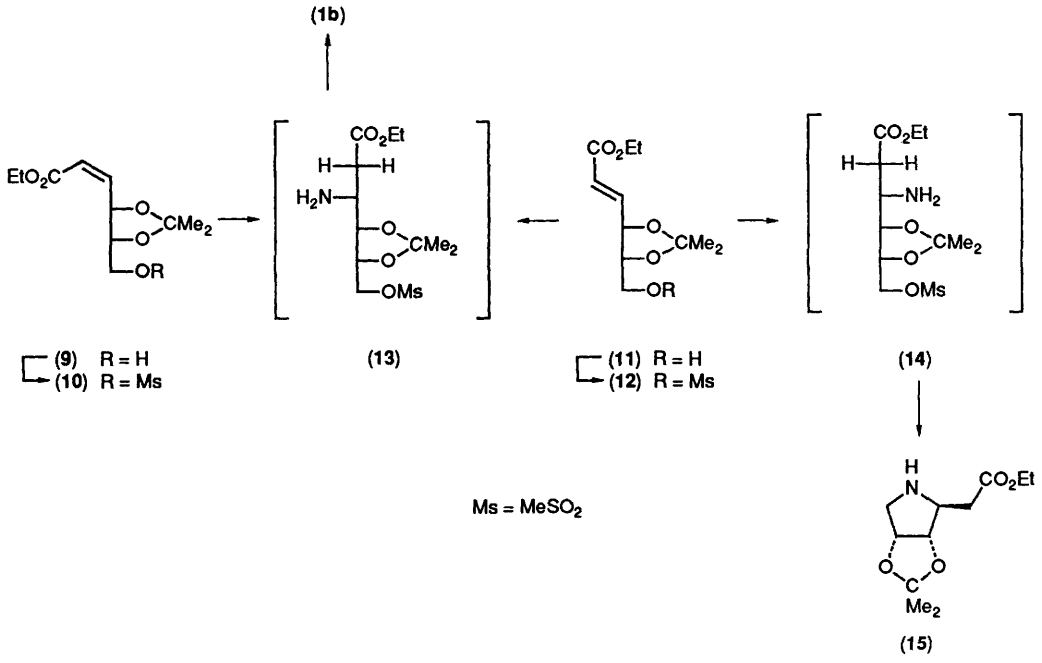
Structure (**18**) was strongly indicated by the values of $J_{3,4}$ and $J_{5,6}$ in the ^1H NMR spectrum.†[2,8,11] In the ^{13}C spectra of

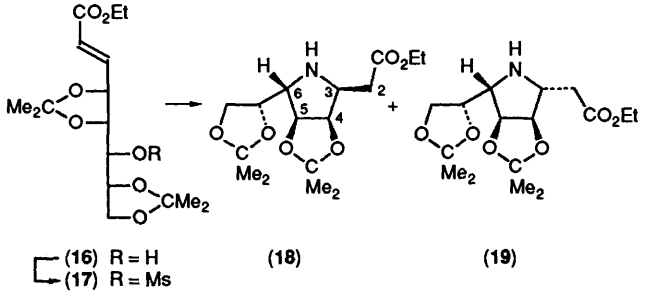


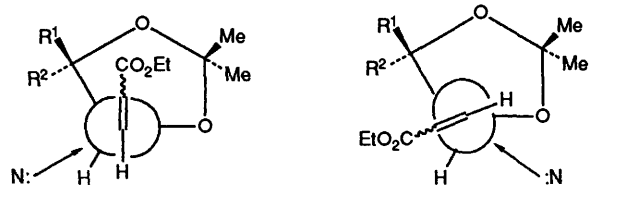
(**18**) and (**19**) the 2-C and 4,5-acetonide acetal signals in (**18**) were shielded relative to those for (**19**), indicating steric compression expected in the *cis* isomer (**18**).[2,8,12]

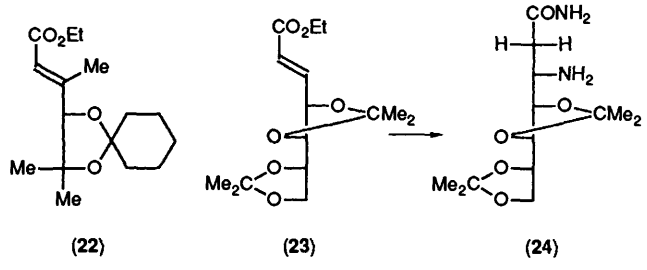
The origin of the diastereoselectivity of the conjugate addition of ammonia and benzylamine in this series of α,β-unsaturated esters has been discussed in a review by McGarvey *et al.*[13] A Felkin-type[14] model (**20**) was proposed to account for

† Selected spectral data. Ethyl 2,3,6-trideoxy-3,6-imino-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-L-*altro*-octonate (**18**); δ_H(200 MHz; $CDCl_3$) 2.58 (2 H, m, $J_{2,3}$ 6.9 Hz, 2-H_2), 3.58 (1 H, dt, $J_{3,4}$ 4.4 Hz, 3-H), 4.45 (1 H, dd, $J_{5,4}$ 5.75, $J_{5,6}$ 0.8 Hz, 5-H); δ_C 34.5 (2-C), 109.5, and 111.6 (CMe_2). Ethyl 2,3,6-trideoxy-3,6-imino-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-L-*allo*-octonate (**19**); δ_C 38.5 (2-C), 109.5, and 114.2 (CMe_2).









the *threo* selectivity of the products. Although such a transition state may account for the result for the *E* isomer of (7) [(**20**) R^1 = H, R^2 = Me] the *Z* isomer of (7) will have strong interactions across the acetal ring in this conformation. Prohibitive interactions will occur in the *erythro* acetals (**4**) [(**20**) R^1 = Me, R^2 = H], (**10**) and (**12**) [(**20**) R^1 = CH_2OMs, R^2 = H], and (**17**) [enantiomer of (**20**) R^1 = alkyl, R^2 = H], particularly for the *Z* isomer (**10**). We suggest for these cases [and possibly for *E*-(7) as well] the alternative transition state (**21**) which resembles the Cornforth model[15,16] and model B_1 of Felkin.[14]

Fuganti and his colleagues[6] found that the unsaturated ester (**22**) was resistant to amination.

We are aware of one exception to the preference for a *threo* product; the αβ-unsaturated ester (**23**) reacts with methanolic ammonia at 100 °C to give mainly the L-*manno* amide (**24**) (*manno*:*gluco*, 2:1),[17] a result confirmed later in the D-series.[18] It should be noted that a *threo* acetal has access to a greater number of stable conformations for the ester group compared to an *erythro* acetal, and other factors, *e.g.* the bulky second acetal group, may be important in this case.

Experimental

Typical Procedures

(E)-*Ethyl* 2,3-*Dideoxy*-4,5-O-*isopropylidene*-6-O-*methylsulphonyl*-D-erythro-*hex*-2-*enonate* (**12**).—To a solution of methanesulphonyl chloride (0.45 ml, 5.61 mmol) in dry pyridine (2 ml) was added dropwise a solution of the alkene (**11**) (430 mg, 1.87 mmol) in dry dichloromethane (4 ml) at 0 °C over 20 min. After reaction overnight water (0.5 ml) was added to destroy excess of acid chloride and the product isolated conventionally using dichloromethane. The resulting syrup was chromatographed on silica.[2] Light petroleum–ether (3:1 ⟶ 1:1) eluted the *sulphonate* (**12**), obtained as a pale yellow syrup (510 mg. 88%); $[\alpha]_D$ −4° (*c* 1.1 in Me_2CO); ν_{max} (film) 1720 (C=O), 1360, and 1170 cm^{-1} (SO_2Me); δ_H (200 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.38 and 1.52 (2 × 3 H, 2 × s CMe_2), 3.03 (3 H, s, SO_2Me), 4.07 (2 H, d, $J_{5,6}$ 6.15 Hz, 6-H_2), 4.20 (2 H, q, *J* 7.1 Hz, CH_2Me), 4.50 (1 H, m, 5-H), 4.86 (1 H, ddd, $J_{4,5}$ 6.7, $J_{4,3}$ 5.25 $J_{4,2}$ 1.6 Hz, 4-H), 6.18 (1 H, dd, $J_{2,3}$ 15.6, $J_{2,4}$ 1.6 Hz, 2-H), 6.82 (1 H, dd $J_{3,2}$ 15.6, $J_{3,4}$ 5.25 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 14.17 (CH_2Me), 25.19 and 27.60 (CMe_2), 37.67 (SO_2Me), 60.73 (CH_2Me), 67.43 (C-6), 75.32 and 75.70 (C-4 and -5), 110.27 (CMe_2), 123.92 (C-2), 140.13 (C-3), and 165.54 (C-1) (Found: $[M-CH_3]^+$ 293.068. $C_{12}H_{20}O_7S$ $-CH_3$ requires *m*/*z* 293.069).

Ethyl 2,3,6-*Trideoxy*-3,6-*imino*-4,5-O-*isopropylidene*-D-arabino-*hexonate* (**1b**) *and Its* D ribo *Epimer* (**15**).—A solution of the sulphonate (**12**) (394 mg, 1.28 mmol) in ethanol (10 ml) was saturated with ammonia at 0 °C. After 96 h at room

temperature the solvent was evaporated and the residue partitioned between aqueous ammonia (30% w/v, 10 ml) and dichloromethane (20 ml). The organic layer was washed with water, dried, and evaporated. The crude product was chromatographed, under nigrogen, on silica doped with triethylamine. Light petroleum–ether (1:1 ⟶ 1:8) gave a mixture of pyrrolidines (**1b**) and (**15**) (238 mg, 81%; ratio 9:1 by ^{1}H NMR). Rechromatography afforded (**1b**) (206 mg, 70%) and (**15**) (23 mg, 8%), indistinguishable from authentic materials.[2]

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