COMMUNICATION

Michael addition of N- and O-centred nucleophiles to tethered acrylates. The role of double bond geometry in controlling the diastereoselectivity of cyclisations leading to 2,6-disubstituted tetrahydropyrans and piperidines

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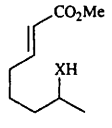
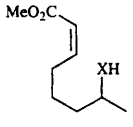
Cyclisation of substrates 1–4 occurs readily to give the corresponding 2,6-disubstituted tetrahydropyran or piperidine. The geometry about the carbon–carbon double bond of the Michael acceptor within the substrate is shown to have a significant impact on the diastereoselectivity of the cyclisation process.

2,6-Disubstituted tetrahydropyran and piperidine ring systems are found embedded within the frameworks of many biologically active natural products and, as a result, they have been the targets of numerous synthetic studies.[1,2] In principle, such systems could be prepared *via* intramolecular Michael addition of an N- or O-centred nucleophile to a tethered acrylate. Furthermore, it is conceivable that the geometry about the carbon–carbon double bond of the Michael acceptor might be exploited so as to control the diastereoselectivity of such cyclisations. Surprisingly, no relevant work appears to have been described.[3] Consequently, we now report that either diastereoisomer of the corresponding 2,6-disubstituted tetrahydropyran or piperidine can be obtained, in a highly diastereoselective fashion, by employing the title reactions and using the appropriate double bond geometry within the acrylate moiety. Intriguingly, for those cyclisations involving an N-centred nucleophile the relationship between the double bond geometry of the substrate and the stereochemistry of the product is exactly opposite to that observed for the analogous process involving an O-centred nucleophile.

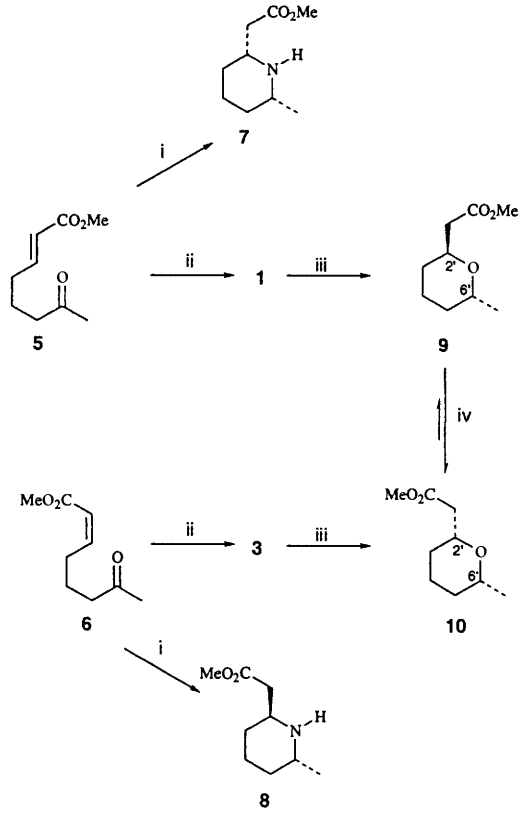


1 X = O
2 X = NH



3 X = O
4 X = NH

The substrates **1–4** required for the present study were readily generated by the reactions shown in Scheme 1. Thus, chemoselective reduction of the ketone moiety within compounds **5**[4] and **6**†‡ was readily achieved using sodium borohydride in methanol and in this way the corresponding alcohols, **1** and **3** respectively, were obtained in high yield. Not surprisingly, attempts to prepare the amino-substituted acrylates **2** and **4** by reductive amination of the same keto compounds resulted in the corresponding piperidines instead. Thus, treatment of compound **5** with a mixture of ammonium acetate and sodium cyanoborohydride in methanol gave the *cis*-2,6-disubstituted piperidine **7**[1] (86%) as the only isolable product. Presumably, amine **2** is the primary reaction product but this undergoes *in situ* Michael addition to give compound **7**. Reductive amination of keto acrylate **6** gave, *via* the intermediate amine **4**, the *trans*-2,6-disubstituted piperidine **8** (73%) as the exclusive product of reaction. The spectroscopic data obtained on each of compounds **7** and **8** were in *full accord*



Scheme 1 *Reagents and conditions:* i, NH_4OAc (10 mmol equiv.), $NaBH_3CN$ (1.1 mol equiv.), MeOH, 60 °C, 16 h; ii, $NaBH_4$ (0.5 mol equiv.), MeOH, 18 °C, 0.25 h; iii, NaH (1.0 mol equiv.), THF, −78 to 18 °C, 1 h; iv, ref. 6

† Compound **6** was prepared by reaction of 5-oxohexanal[4] with methyl bis(trifluoroethyl)phosphonoacetate, potassium carbonate and the 18-crown-6-acetonitrile complex as described by Still and Gennari.[5]
‡ All new compounds had spectroscopic data (IR, NMR, mass spectrum) consistent with the assigned structures. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for all new substances and/or suitable derivatives.

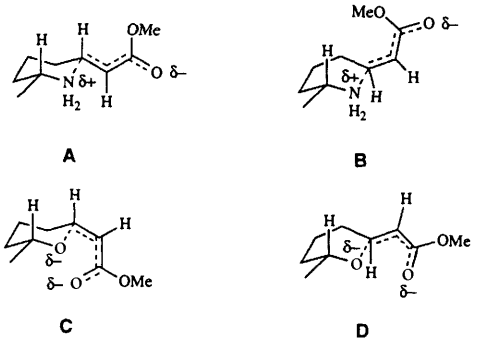


Fig. 1

with the assigned structure. Furthermore, the spectral data obtained on the former cyclisation product, **7**, were in excellent agreement with those derived from authentic (+)-**7**.§

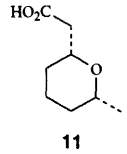
Cyclisation of compound **1** was readily effected with sodium hydride in tetrahydrofuran at −78 to 18 °C.[3] After 1 h the starting material had been completely consumed and work-up provided a mixture of the *trans*-2,6-disubstituted tetrahydropyran **9**[6–9] (72%) and the isomeric *cis*-compound **10**[6–9] (26%) (see Experimental section). Cyclisation of substrate **3** was effected under the same conditions as used for isomer **1** and, in dramatic contrast to the previous result, a 97:3 mixture of tetrahydropyrans **10** and **9** was obtained (98% combined yield).¶

Transition state structures which would account for the observed outcomes of the cyclisations detailed above are given in Fig. 1. Thus, conversion of amine **2** into piperidine **7** might involve the extended chair-like structure **A** while cyclisation of amine **4** to compound **8** can be rationalised by invoking a boat-like transition state **B**. The essentially exclusive conversion of the sodium salt of (*Z*)-acrylate **3** into the *cis*-2,3-disubstituted tetrahydropyran **10** may be proceeding under conditions in which a transition state structure such as **C** plays a major role. Structure **C** should be stabilised to some extent because chelation of the participating sodium ion between two partially negatively charged oxygens is possible. This type of argument raises the possibility that different metal atoms may exert differing effects on the diastereoselectivity of such cyclisations. To test such a possibility compounds **1** and **3** were reacted with LiH and KH (instead of NaH) but no dramatic differences in outcome were observed. However, a more extended survey of metal–ion effects seems warranted.

The reaction of the sodium salt of (*E*)-acrylate **1** to give a *ca.* 3:1 mixture of **9** and **10** represents the least selective of the four cyclisations described here. It would appear that this outcome is a reflection of an inherently less selective cyclisation process since, under the reaction conditions, the *trans*-cyclisation product **9** is not converted into the thermodynamically more stable *cis*-isomer **10**.[6] The boat-like transition state **D** which could be invoked to account for the preferential formation of tetrahydropyran **9** from precursor **1** would not, from inspection of molecular models, appear to be capable of as tight metal chelation as transition state **C**. Consequently, it is conceivable that there might be some stereochemical leakage in the cyclisation of substrate **1** *via* a transition state equivalent to **A**.

§ It has recently been shown[1] that (+)-**7** can be readily converted into the alkaloids (+)-pinidinone and (+)-monomorine. Consequently, the acquisition of (±)-**7**, as described above, constitutes formal total syntheses of the racemic modifications of these natural products.

¶ The acquisition of significant quantities of the methyl ester **10** by this route has allowed for completion of a concise synthesis of the racemic modification of the natural product (*S*,*S*)-(*cis*-6′-methyltetrahydropyran-2′-yl)acetic acid (+)-**11**, a perfumery compound isolated from the glandular secretions of the civet cat (*Viverra civetta*).[6] Thus, a purified sample of ester **10** was hydrolysed, under previously specified conditions,[6] to give (±)-**11** (93%, mp 53 °C; lit.,[6] mp 52–53 °C). The physical and spectroscopic properties of this material were in excellent agreement with the analogous data reported previously.[6–8]



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Experimental

Cyclisation of compound 1

A magnetically stirred suspension of sodium hydride (117 mg of a 60% dispersion in mineral oil, 2.9 mmol) in tetrahydrofuran (15 ml) was cooled to −78 °C while being maintained under a nitrogen atmosphere. Methyl (*E*)-7-hydroxyoct-2-enoate **1** (500 mg, 2.9 mmol) in tetrahydrofuran (5 ml) was injected *via* syringe after which the reaction mixture was allowed to warm to room temperature (*ca.* 18 °C) over 1 h, then diluted with water (50 ml) and extracted with diethyl ether (3 × 30 ml). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to MPLC (silica, 15:85 ethyl acetate–hexane elution) afforded two major components (R_f 0.8 and 0.7).

Concentration of the fractions containing the less mobile component gave methyl (±)-(*trans*-6-methyltetrahydropyran-2-yl)acetate **9** (350 mg, 70%) as a clear colourless oil (Found: $M^{+\bullet}$, 172.1097. $C_9H_{16}O_3$ requires *M*, 172.1099); ν_{max}(NaCl) 2968, 1737, 1435, 1285, 1210, 1165, 1136, 1047, 1023 cm^{-1}; δ_H 4.25 (m, 1 H, H2′), 3.88 (m, 1 H, H6′), 3.66 (s, 3 H, OMe), 2.65 (dd, *J* 15 and 8 Hz, 1 H, H2), 2.42 (dd, *J* 15 and 7 Hz, 1 H, H2), 1.77–1.55 (complex m, 4 H), 1.43–1.20 (complex m, 2 H) and 1.14 (d, *J* 6 Hz, 3 H, Me); δ_C 171.9, 67.9, 67.5, 51.6, 38.9, 31.2, 29.6, 19.5 and 18.2; *m*/*z* (70 eV) 172 (4%, $M^{+\bullet}$), 130 [34, $(M - MeOH)^{+\bullet}$], 129 (41), 116 (71), 99 (100), 54 (91).

Concentration of the fractions containing the more mobile component gave methyl (±)-(*cis*-6-methyltetrahydropyran-2-yl)acetate **10** (140 mg, 28%) as a clear colourless oil (Found: $M^{+\bullet}$, 172.1102. $C_9H_{16}O_3$ requires *M*, 172.1099); ν_{max}(NaCl) 2968, 2931, 2858, 1738, 1435, 1371, 1342, 1285, 1203, 1169, 1086, 1072, 1042 cm^{-1}; δ_H 3.75 (m, 1 H, H2′), 3.66 (s, 3 H, OMe), 3.44 (m, 1 H, H6′), 2.54 (dd, *J* 15 and 8 Hz, 1 H, H2), 2.37 (dd, *J* 15 and 7 Hz, 1 H, H2), 1.82–1.73 (complex m, 1 H), 1.66–1.42 (complex m, 3 H), 1.26–1.06 (complex m, 2 H) and 1.12 (d, *J* 6 Hz, 3 H, Me); δ_C 171.8, 74.2, 74.0, 51.5, 41.5, 32.9, 30.9, 23.4 and 22.0; *m*/*z* (70 eV) 172 (9%, $M^{+\bullet}$), 130 [34, $(M - MeOH)^{+\bullet}$], 129 (47), 116 (77), 99 (87), 54 (100).

Acknowledgements

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References

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3 Martín and co-workers (J. M. Palazon, M. A. Soler, M. A. Ramirez and V. S. Martín, *Tetrahedron Lett.*, 1993, **34**, 5467 and references cited therein) have reported on the use of intra-molecular Michael addition for the preparation of 2,3-disubstituted tetrahydropyrans. Mandai *et al.* (T. Mandai, M. Ueda, K. Kashiwagi, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, 1993, **34**, 111) have described the intramolecular 1,4-addition of oxyanions to tethered α,β-unsaturated sulfoxides as a method for preparing, in a diastereoselective fashion, 2,6-disubstituted tetrahydropyrans. Machinaga and Kibayashi (N.

Machinaga and C. Kibayashi, *Tetrahedron Lett.*, 1993, **34**, 5739) have exploited the title reaction as a key step in a synthesis of (+)-decarestrictine L (a 2,3,6-trisubstituted tetrahydropyran) but did not examine the impact of double bond geometry on the diastereoselectivity of the cyclisation process. For an example of a related reaction involving a nitrogen-centred nucleophile see S. Knapp and J. J. Hale, *J. Org. Chem.*, 1993, **58**, 2650.
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9 In the original[6] and two subsequent syntheses of compound **11** (F. W. Lichtenthaler, F. D. Klinger and P. Jarglis, *Carbohydr. Res.*, 1984, **132**, C1; V. Ragoussis and V. Theodorou, *Synthesis*, 1993, 84) intramolecular Michael addition of an oxyanion to a tethered acrylate was employed as the key step. However, in none of these cases was it possible to determine the impact of double-bond geometry on the diastereoselectivity of the cyclisation reaction.

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