# 7-Methyl-2,3,4,5-tetrahydro-1,4-oxazepin-5-one and the Dioxepinone Analogue: Diastereofacial Selectivity in Catalytic Hydrogenation and the Explanation

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Catalytic hydrogenation of the title compound proceeds from the site *anti* to the 7-methyl group to give the *cis*-dimethyl derivative; a possible stereoelectronic effect accounting for this selectivity is proposed based on the conformational analysis of the substrate by X-ray crystallography.

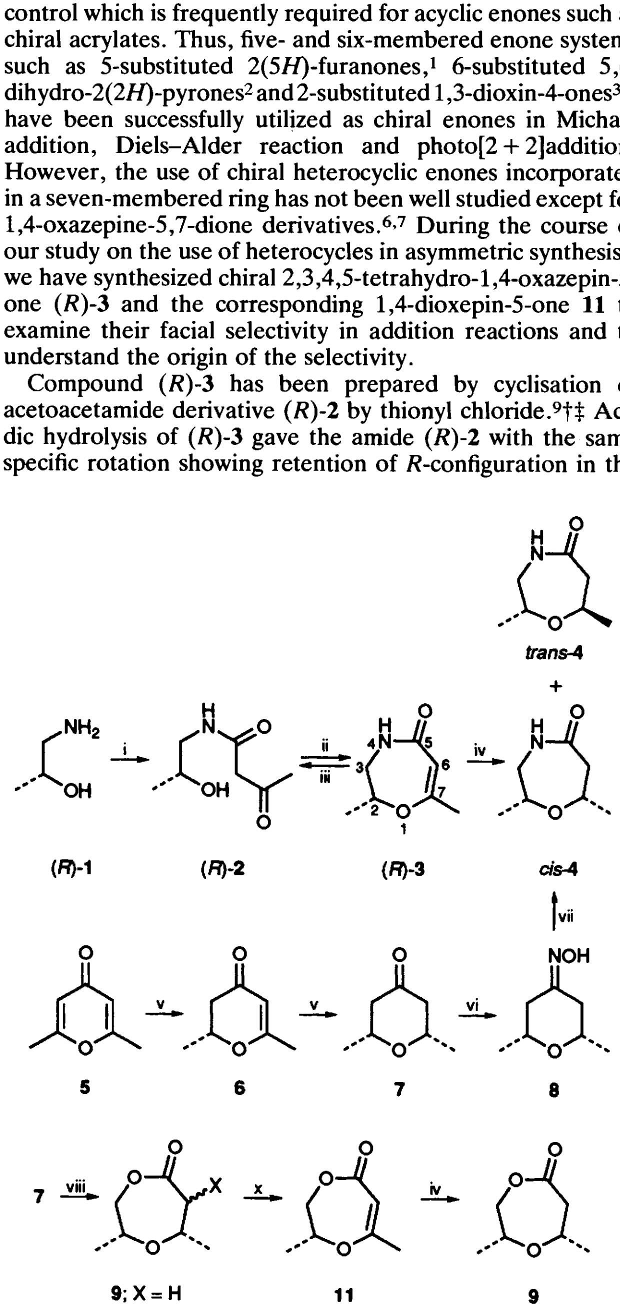
Chiral heterocyclic enones are useful intermediates for enantioselective synthesis. Owing to their rigid conformation, they show high diastereofacial selectivity without chelation control which is frequently required for acyclic enones such as chiral acrylates. Thus, five- and six-membered enone systems such as 5-substituted 2(5*H*)-furanones,[1] 6-substituted 5,6-dihydro-2(2*H*)-pyrones[2] and 2-substituted 1,3-dioxin-4-ones[3–5] have been successfully utilized as chiral enones in Michael addition, Diels–Alder reaction and photo[2 + 2]addition. However, the use of chiral heterocyclic enones incorporated in a seven-membered ring has not been well studied except for 1,4-oxazepine-5,7-dione derivatives.[6,7] During the course of our study on the use of heterocycles in asymmetric synthesis,[8] we have synthesized chiral 2,3,4,5-tetrahydro-1,4-oxazepin-5-one (*R*)-**3** and the corresponding 1,4-dioxepin-5-one **11** to examine their facial selectivity in addition reactions and to understand the origin of the selectivity.

Compound (*R*)-**3** has been prepared by cyclisation of acetoacetamide derivative (*R*)-**2** by thionyl chloride.[9]†‡ Acidic hydrolysis of (*R*)-**3** gave the amide (*R*)-**2** with the same specific rotation showing retention of *R*-configuration in the cyclisation. Catalytic hydrogenation of (*R*)-**3** with Raney Ni gave *cis*-**4** as the sole product in a quantitative yield.‡ The hydrogenation using more active catalysts gave stereoisomixtures (*cis*-**4** : *trans*-**4** 98 : 2 with 10% Pd-C; 92 : 8 with $PtO_2$) as indicated by 500 MHz $^1H$ NMR analysis. Structural assignment of *cis*-**4** was made in a racemic form by the comparison with the authentic sample[10] prepared from oxime **8** as illustrated in Scheme 1. It should be noted that the hydrogenation of dihydropyrone **6**,[11] obtained by partial hydrogenation of **5**, also proceeded in a quantitative yield with complete selectivity.

The dioxepinone **11** was readily prepared in a racemic form starting from compound **7** by Baeyer–Villiger reaction followed by dehydrogenation with a standard method. Catalytic hydrogenation of **11** with Raney Ni afforded *cis*-dimethyl derivative **9** in a quantitative yield. Inspection of 500 MHz $^1H$ NMR spectrum of the product revealed that none of the *trans*-isomer was formed.

The facial selectivity of (*R*)-**3** and **11** is particularly interesting, because the face *syn* to $C_2$–H in **3** is more hindered than the other face as evidenced by X-ray crystallographic analysis (Fig. 1).§,¶ A similar facial selectivity observed in hydrogenation of the chiral 1,3-dioxin-4-one has been explained by pyramidalization of the reacting sp[2] centre.[4] However, no pyramidalization is observed at 7-position of (*R*)-**3** in the X-ray analysis indicating that another origin of selectivity operates.

Though in rare cases the conformation observed in the



**Scheme 1** *Reagents and conditions*: i, diketene, $CH_2Cl_2$, −78 °C; ii, $SOCl_2$ (1.1 equiv.), $CHCl_3$, 0 °C → room temp.; iii, 2 mol $dm^{-3}$ HCl; iv, $H_2$, 50 atm, Raney Ni, 50 °C, EtOH; v, $H_2$, 1 atm, 10% Pd/C, room temp., EtOH; vi, $NH_2OH$; vii, polyphosphoric acid, 80 °C; viii, *m*CPBA, $CH_2Cl_2$; ix, LDA then PhSeCl, THF, −78 °C; x, $O_3$, $CH_2Cl_2$, −78 °C → room temp.

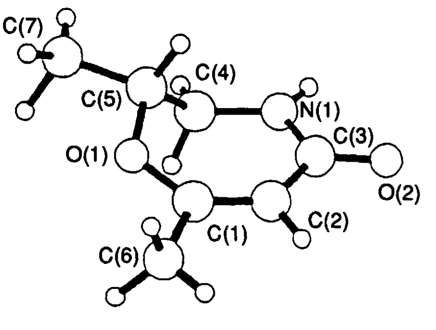
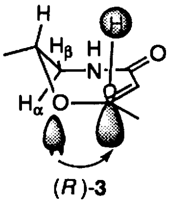
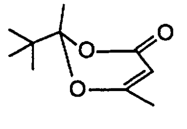


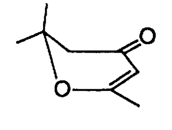
**Fig. 1** Molecular structure of (*R*)-**3**. Selected bond length (Å) and angles (°): O(1)–C(1) 1.337(6); O(1)–C(5) 1.444(4); O(2)–C(3) 1.237(6); N(1)–C(3) 1.335(6); N(1)–C(4) 1.432(6); C(1)–C(2) 1.346(7); C(1)–C(6) 1.519(8); C(2)–C(3) 1.471(7); C(4)–C(5) 1.520(7); C(5)–C(7) 1.523(8); C(1)–O(1)–C(5) 119.9; O(1)–C(1)–C(2) 130.6(4); O(1)–C(1)–C(6) 109.2(4); C(2)–C(1)–C(6) 120.1(4); C(1)–C(2)–C(3) 133.3(4); O(2)–C(3)–C(2) 118.0(4); O(2)–C(3)–N(1) 121.1(4); N(1)–C(3)–C(2) 120.9(4); C(3)–N(1)–C(4) 124.6(4); N(1)–C(4)–C(5) 113.4(4); O(1)–C(5)–C(4) 111.5(4); O(1)–C(5)–C(7) 103.8(4); C(4)–C(5)–C(7) 112.2.



(*R*)-**3**



**12**



**6**

crystalline state is not always the preferred conformation in solution,[12] we propose at present that the most probable reason to account this selectivity is the stereoelectronic effects originally proposed by Cieplak *et al.*[13] Namely, the β-face attack may be facilitated by the interaction of oxygen lone pairs [*n*O(1)] with an antibonding orbital of the incipient bond [σ*C(7)–H]. This explanation is equally applicable not only for the hydrogenation of **11** but also for similar selectivities observed in the hydrogenation of **6** as well as **12**. The high diastereofacial selectivity of (*R*)-**3** and **11** well suggests that they can serve widely as chiral enones.

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## Footnotes

[†] All new compounds exhibited satisfactory spectroscopic ($^1$H NMR, IR, UV) and combustion or high resolution mass spectral analytical data.

[‡] (*R*)-**3**: mp 78–80 °C; $[\alpha]_D^{24}$ +112.8 (*c* 1, $CHCl_3$); (*R*)-**2**: mp 40–42.5 °C; $[\alpha]_D^{24}$ −32.8 (*c* 2.05, $CHCl_3$); *cis*-**4**: mp 149–149.5 °C; $[\alpha]_D^{22}$ +22.6 (*c* 1, $CHCl_3$).

[§] Crystals from hexane–diethyl ether had space group symmetry $P2_12_12_1$ and cell constants of $a$ = 8.215(2), $b$ = 24.693(1), $c$ = 7.526(5) Å and contained eight molecules, leading to a calculated density of 1.228 g cm$^{-3}$. A total of 1350 unique reflections were measured at 298 K on a Rigaku AFC-5R automated diffractometer with graphite-monochromated Cu-*K*α-radiation, of which 1171 with $|F_0| > 3\sigma|F_0|$ were used in the refinement. The intensities were corrected for Lorentz and polarization factors, but not for absorption and second extinction. The final *R* value was 0.049. Atomic coordinates, bond length and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

[¶] $^1$H NMR spectroscopic study well showed that the conformation of *R*-**3** shown in Fig. 1 is retained also in solution as evidenced by the following coupling constants: $J_{2\text{-H-3H}_\beta}$ 0 $J_{2\text{-H-3H}_\alpha}$ 6.0 Hz (see Fig. 2).

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