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Chiral 6,7-Dihydrooxepin-2(5*H*)-ones and the Azepinone Analogues: Conformation and Diastereofacial Selectivity in Addition to the Enones

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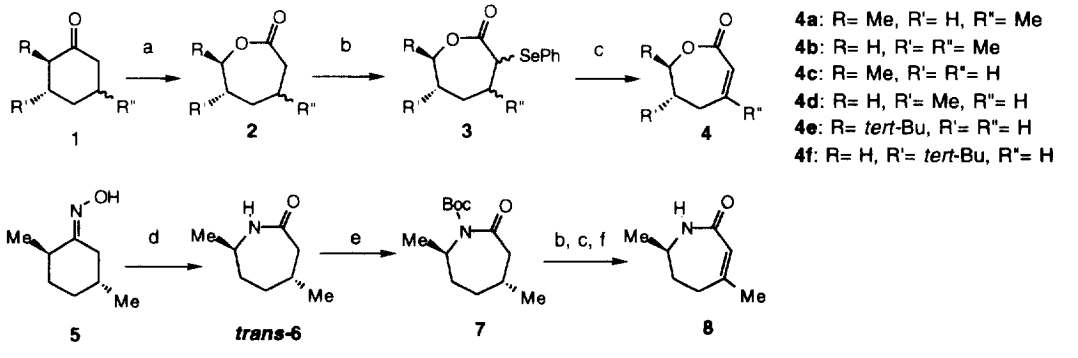
Abstract: Diastereofacial selectivity in addition to the enones of 6-and 7-substituted dihydrooxepinones was studied. The addition occurred preferentially from the face anti to the substituent and 7-substituted substrates showed higher diastereofacial selectivity than the 6-substituted substrates. An explanation for the observed diastereofacial selectivity is proposed.

Chiral heterocyclic enones are useful intermediates not only for diastereoselective synthesis but also for enantioselective synthesis. Owing to their rigid conformations, they show high diastereofacial selectivity without chelation control which is usually required for acyclic enones such as chiral acrylates. Thus, five- and six-membered heterocyclic compounds 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[3,4] have been successfully utilized as chiral enones in Michael addition, Diels-Alder reaction, and photo[2+2]addition. The high diastereofacial selectivity has been also observed in enones incorporated in much larger rings such as 9- to 12- membered lactones.[5] However, the diastereofacial selectivity of chiral heterocyclic enones incorporated in a seven-membered ring has not been extensively studied.[6,7] Here we report the diastereofacial selectivity of 6- and 7-substituted dihydrooxepinones and 7-substituted dihydroazepinone in addition to the enone moieties.

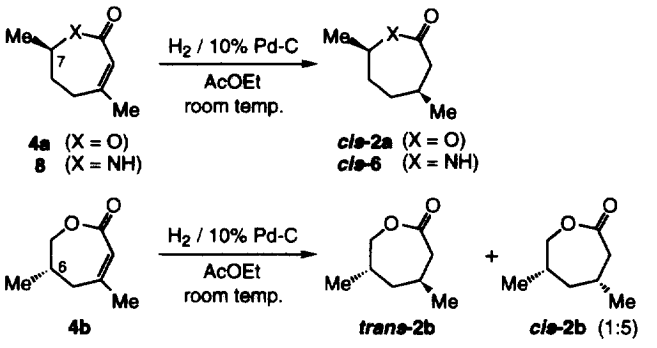
All chiral oxepinones and azepinone were prepared as racemic mixtures by the method illustrated in Scheme 1,[8] since in this study only the relative stereochemistry of the stereogenic center in the products was of interest.



4a: R= Me, R'= H, R"= Me
4b: R= H, R'= R"= Me
4c: R= Me, R'= R"= H
4d: R= H, R'= Me, R"= H
4e: R= *tert*-Bu, R'= R"= H
4f: R= H, R'= *tert*-Bu, R"= H

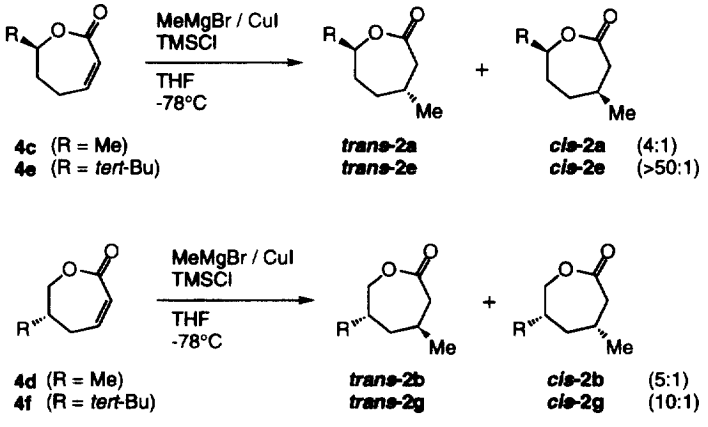
Scheme 1 : a, *m* CPBA, CH_2Cl_2; b, LDA then PhSeBr, THF, -78°C; c, O_3 or H_2O_2, CH_2Cl_2; d, PCl_5, CH_2Cl_2 ; e, $(Boc)_2O$, DMAP, benzene; f, CF_3COOH

On catalytic hydrogenation with 10% Pd-C in ethyl acetate, 4,7-dimethyloxepinone (**4a**) and the azepinone analogue (**8**) afforded exclusively the *cis*-dimethyl compounds *cis*-**2a** and *cis*-**6** in quantitative yields, respectively, while 4,6-dimethyloxepinone (**4b**) afforded a mixture of *trans*-**2b** and *cis*-**2b** (95% yield) in 1:5 ratio as revealed by ^{1}H-NMR (500 MHz) spectroscopic study. The assignment of the hydrogenated products was done by comparison of the ^{1}H-NMR data with those of authentic samples.



Scheme 2

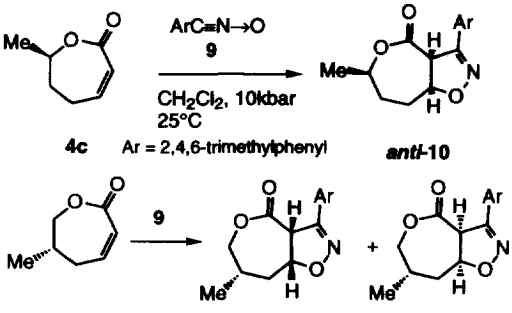
On conjugate addition reaction with methylmagnesium bromide in the presence of CuI and chlorotrimethylsilane at -78 °C, **4c** gave *trans*-**2a** and *cis*-**2a** in 4:1 ratio, while the *tert*-butyl derivative **4e** gave exclusively *trans*-**2e**. Under the same conditions, **4d** gave a mixture of *trans*-**2d** and *cis*-**2d** (81% yield) in a ratio of 5:1, and the *tert*-butyl derivative (**4f**) gave a mixture of *trans*-**2g** and *cis*-**2g** (82% yield) with an improved ratio of 10:1.



Scheme 3

The result shows that both 7-substituted oxepinones and the 6-substituted isomers display *anti*-selectivity in catalytic hydrogenation and conjugate addition. Moreover, it has been demonstrated that 7-substituted substrates show a higher diastereoafacial selectivity than the 6-substituted isomers, and introduction of the bulkier *tert*-butyl group to the chiral center results in an improved stereoselectivity.

Finally, the diastereofacial selectivity of chiral oxepinones in a cycloaddition reaction was examined. The reaction of 2,4,6-trimethylbenzonitrile *N*-oxide (**9**) with **4c** proceeded under highpressure (10 kbar) for one day at room temperature to afford *anti*-**10** as the sole product in 95% yield. The regio- and stereochemistries were determined by X-ray crystallographic analysis (Fig.1).[9] As expected, this cycloaddition occurred at the face *anti* to the methyl substituent. In contrast, compound **4d** exhibited no diastereofacial selectivity in the reaction with **9** affording a 1:1 mixture of *syn*-**12** and *anti*-**12** as shown by ^{1}H-NMR analysis of the reaction mixture.



Scheme 4

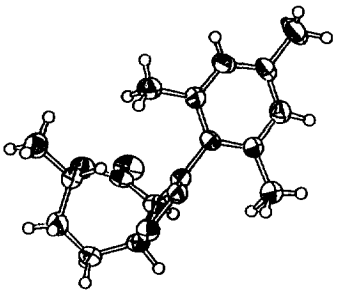


Fig.1 Molecular structure of *anti*-10

It is clear that the asymmetric induction in these seven-membered enones is not caused by direct steric interaction between the substituent at the chiral center and reagents, as evidenced by the higher asymmetric induction in the 7-substituted substrates in which the steric interaction is less than that in the 6-substituted substrates. To rationalize the above result, compound **8** (mp 93-94 °C) was subjected to X-ray crystallographic analysis. As shown in Fig. 2, this compound has an envelope conformation in which all of the ring atoms except for C_6 are almost in a plane and the 7-methyl group takes *pseudo*-equatorial orientation.[9] This conformation is very similar to that of oxazepinone derivative (**13**)[6] with a methyl group at the stereogenic center in *pseudo*-equatorial position. These envelope conformations are originated from the coplanarity of the amide group and the conjugated enone group. Therefore, it is reasonable to assume that 6-and 7-substituted oxepinones take envelope conformations (**4a~f**) as illustrated in Fig. 2. The alternative envelope conformations (**4'**) are less favorable due to the steric reason. Semi-empirical calculations (MOPAC PM3)[10] suggested that conformations **4a** and **4b** (minimum energy conformations) are more stable than **4'a** and **4'b** by 0.67 and 1.98 Kcal/mol, respectively. The calculation also suggested that conformations **4e** and **4f** are more stable than **4'e** and **4'f** by 3.41 and 5.88 Kcal/mol, respectively.^{1}H-NMR (500 MHz) spectroscopic study well supported the conformations of **4a~f** as well as **8** in solution as evidenced by the following coupling constants :$J_{7H\alpha\text{-}6H\beta}$ =7.0~9.0 Hz, $J_{7H\alpha\text{-}6H\alpha}$=1.5~2.5 Hz for **4a**, **c**, **e** and **8**; $J_{7H\alpha\text{-}6H\beta}$=7.0~8.0 Hz, $J_{7H\beta\text{-}6H\beta}$=1.5~2.0 Hz for **4b**,**d**,**f**; $J_{7H\beta\text{-}6H\beta}$=1.5 Hz for **4f**.

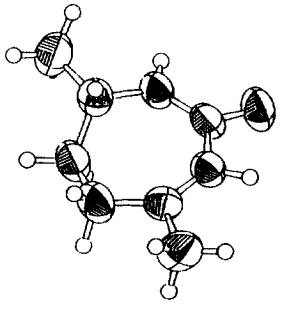
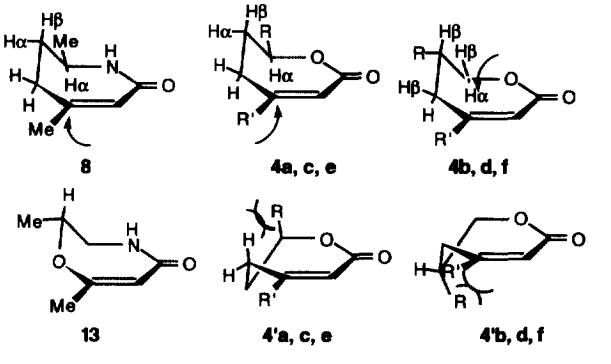
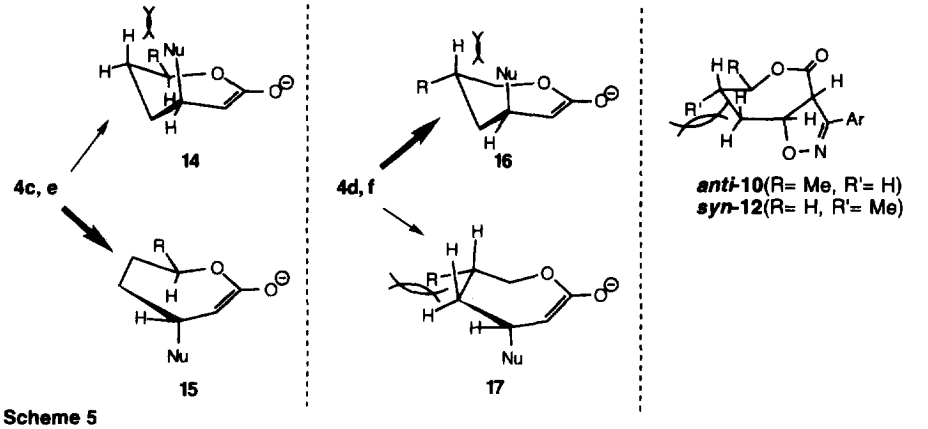


Fig. 2 Molecular Structure of **8**



Although the reasons for the above selectivity have not been clearly established, we might assume that the selectivity is caused mostly by steric requirements in the transition state.[11] For example, conjugate addition to **4c** and **4e** occurs preferentially at the less hindered bottom face to give stable intermediate **15**. However, the

bottom face attack to **4d** and **4f** leads to intermediate **17** which is less stable than **15** due to the eclipsing interaction of the R' substituent. For this reason, addition to **4d** and **4f** occurs selectively at the top face. The improved top face selectivity in the *tert*-butyl derivative **4f** supports this assumption. The selectivity in the cycloaddition is rationalized similarly; destabilization of *syn*-**12** by the R' substituent allows the attack at both of the faces (Scheme 5).



Scheme 5

In conclusion, we have shown that addition to the enone moiety of 6- and 7-substituted dihydrooxepinones occurs selectively from the face *anti* to the substituent. The diastereofacial selectivity is believed to arise from steric requirements in the transition state.

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8. All new compounds exhibited satisfactory spectroscopic (^{1}H-NMR and IR) and combustion or high resolution mass spectral analytical data.
9. Full details of the crystal structure investigation of **8** and *anti*-**10** have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, UK.
10. MOPAC PM3 was implemended on a Tektronix CAChe workstation.
11. A similar rationalization has been proposed for diastereofacial selectivity in addition to chiral 6-membered cyclic enones such as 2-cyclohexen-1-ones and 5,6-dihydro-2(2*H*)-pyrones. See: Deslongchamp, P.; *Stereoeletronic Effects in Organic Chemistry*, Pergamon, Oxford, 1983, p.209. Takano, S.; Setoh, M.; Ogasawara, K., *Tetrahedron: Asymmetry*, 1992, **3**, 533.

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