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Studies on 1,3-Allylic Strain Control on Dihydroxylations and Hydrogenations of α-Substituted Enoates

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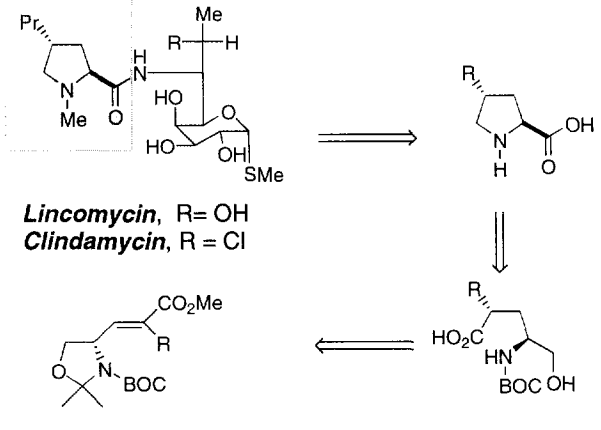
Abstract: L-serine derived enoates **8** and **9** were subjected to catalytic dihydroxylation and hydrogenation reactions. The observed selectivities can be explained to arise from 1,3-allylic strain.

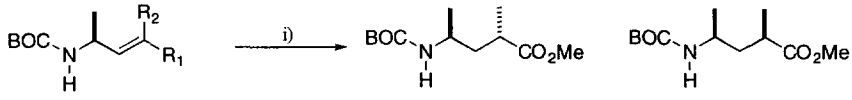
In conjunction with our efforts to asymmetric synthesis of Lincomycin type antibiotics, we needed an efficient method for the synthesis of 4-*n*-propyl proline fragment. Retrosynthetic analysis of the 4-substituted proline structure revealed that serine derived α-substituted enoates could be used as starting compounds. The concept of allylic 1,3- ($A^{1,3}$)- strain is a powerful tool in explaining conformational organization in acyclic systems and has aided chemists in achieving high levels of asymmetric induction in a predictable manner.[1] Recently, in conjunction with the synthesis of C_{26}-C_{32} fragment of calyculins, L-alanine derived α-methyl-substituted enoates **1a,b** were subjected to catalytic hydrogenation and the observed selectivity was explained to arise from $A^{1,3}$-strain (Scheme 2).[2] We have previously shown that OsO_4-catalysed dihydroxylation of cyclically protected L-serine (or L-threonine) derived *Z*-enoate **4a** gives the desired *anti,anti*-diastereomer **5a** as the sole product, whereas the corresponding *E*-enoates give ~1:1 mixtures of *anti,syn*- and *syn,syn*-diastereomers (Scheme 3).[3] This selectivity was also explained to arise from steric control (due to $A^{1,3}$-strain) in the *Z*-olefin. However, the $A^{1,3}$- strain control is lost in the corresponding acyclically protected *Z*- or *E*-enoates as dihydroxylation proceed with only poor selectivity (Scheme 2 **4b**, **5b**, **6b**).[4]



Scheme 1.

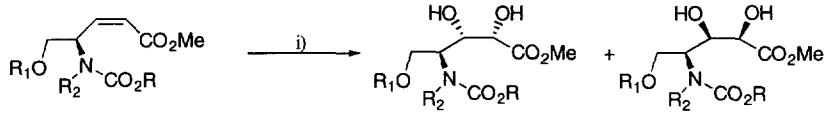
Based on these results we assumed that hydrogenation of the cyclically protected α-alkyl substituted enoates should show facial selectivity due to $A^{1,3}$-strain control. We decided to prepare methyl-substituted

enoates **8** and **9** and subject them to catalytic hydrogenation to find out if the outcome could be explained by the principle of the allylic 1,3-strain.



1a R_1=CO_2Me, R_2=Me
1b R_1=Me, R_2=CO_2Me

Scheme 2. Reagents: i) H_2, Pd/C (cat.), MeOH

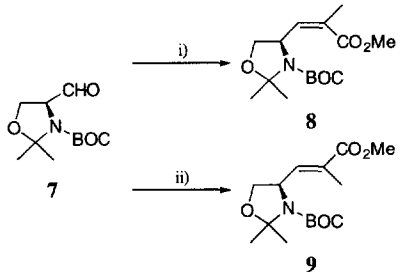


4a R_1, R_2 = $C(Me)_2$
4b R_1= Me, R_2 = H

Scheme 3. Reagents: i) OsO_4, NMO, Me_2CO, H_2O.

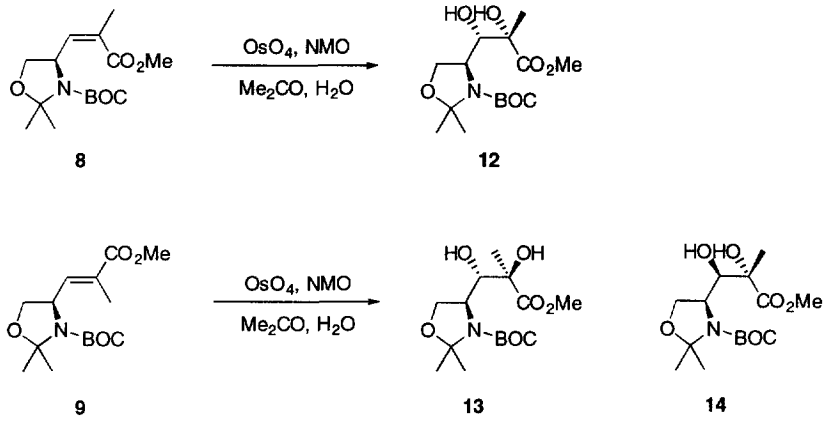
We were also interested in how the alkyl substituent would affect the selectivity *e.g.* in dihydroxylation of the *E*-enoate **9**, because allylic strain control was lost in the corresponding unsubstituted *E*-enoate as shown in Scheme 3.

The preparation of enoates **8** and **9** is shown in Scheme 4. The *Z*-enoate **8** was synthesized with high selectivity (98%, *Z*:*E* >90:1) from the L-serine derived aldehyde **7** and bistrifluoroethyl phosphonate **10** utilizing methodology employed previously in our laboratory .[2c,4,5,6,7] Olefination of aldehyde **7** with phosphorane **11** gave the *E*-enoate **9** with good selectivity (95%, *E*:*Z* 96:4).[8]



Scheme 4. Reagents and conditions: i) 18-C-6, K_2CO_3, $(CF_3CH_2O)_2P(O)CH(Me)CO_2Me$ (**10**), toluene, -20 to 0°C, 16h; ii) $Ph_3PC(Me)CO_2Me$ (**11**), CH_2Cl_2, 0°C, 16h

Compounds **8** and **9** were then dihydroxylated by catalytic osmylation (Scheme 5). Reactions were performed with OsO_4/NMO under standard conditions[9] (5 and 8 days). Dihydroxylation of the *Z*-enoate **8** gave a single diastereomer **12** as expected.[10] Reaction of **9** gave two diastereomers **13** and **14** in a 3:1 ratio. We rationalize these results by the fact that the methyl group in **9** causes less allylic strain and allows the olefinic bond to rotate more freely than the methyl ester group in **8**.



Scheme 5.

Hydrogenations were then performed with Pd/C in various solvents (MeOH;EtOH, EtOAc, hexane) but proceeded with inferior selectivity (Table).[11] Only a slight preference for the desired *syn*-products was observed (5:3 *syn*:*anti* for **8** and 3:4 *syn*:*anti* for **9**).[12,13] The erosion of selectivity is most likely due to isomerisation of the alkene, which often accompanies the addition of hydrogen.[14] Among the platinum group metals palladium has the highest tendency to promote isomerisation.[15] To avoid the isomerisation, platinum, which should have better ability to give primarily *cis*-delivery of hydrogens, was used instead as the catalyst. Improved selectivity was indeed observed (Table).

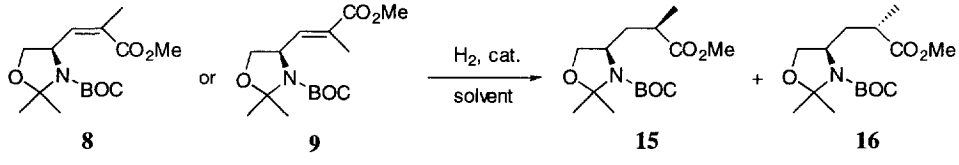


Table.

Entry	Starting material	Catalyst	Solvent	Ratio **15**:**16**
1	**8**	Pd/C	MeOH	5:3
2	**8**	Pt/C	MeOH	3:1
3	**8**	Pt/C	EtOAc	2:1
4	**8**	Pt/C	hexane	5:1
5	**9**	Pd/C	MeOH	3:4
6	**9**	Pt/C	MeOH	1:3
7	**9**	Pt/C	EtOAc	1:5
8	**9**	Pt/C	hexane	1:4

The best selectivity for **8** was achieved when hydrogenation was performed in hexane, whereas **9** gave comparable selectivities in ethyl acetate and hexane. However, no significant solvent effects can be observed, whereas changing the catalyst from Pd to Pt improved selectivity remarkably.

We conclude that **8** and **9** can be hydrogenated with good selectivity resulting in a new stereocenter, whose stereochemistry can be predicted by $A^{1,3}$-strain control. This method is now being applied in our laboratories for the synthesis of 4-substituted prolines and will be reported in due course.

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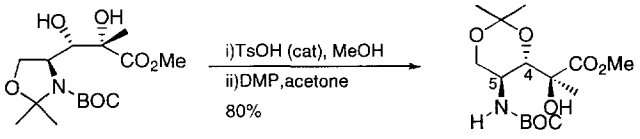
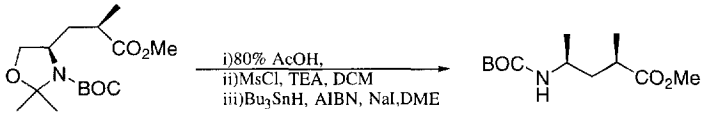
REFERENCES AND NOTES

1. a) Hoffmann, R.W. *Chem. Rev.* **1989**, *89*, 1841. b) Cha, J.K.; Kim, N.-S. *Chem Rev.* **1995**, *95*, 1761.
2. Koskinen, A.M.P.; Pihko, P.M. *Tetrahedron Lett.* **1994**, *35*, 7417.
3. a) Koskinen, A.M.P. *Pure & Appl. Chem.* **1995**, *67*, 1031. b) Koskinen, A.M.P.; Chen, J. *Tetrahedron Lett.* **1991**, *32*, 6977. c) Koskinen, A.M.P.; Otsomaa, L. manuscript in preparation.
4. Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett*, **1992**, 703.
5. Garner, P.; Park, J.M. *J.Org, Chem.* **1990**, *55*, 3772.
6. Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
7. Koskinen, A.M.P.; Koskinen, P.M. *Synlett*, **1993**, 501.
8. All new compounds gave satisfactory spectral and analytical (HRMS or elemental analysis) data.
9. a) Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. b) Christ, W.J.; Cha, J.K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.
10. Diastereoselectivities of hydrogenations were determined by HPLC. Stereochemistry of diol **12** was proven by converting it to the corresponding six membered O,O-acetonide **17** and its ^{1}H-NMR spectra were analyzed . Observed vicinal coupling constant of 9.9 Hz between H-5 and H-4 indicated the stereochemistry be as shown.



12 **17**

11. Illustrative hydrogenation: **9** was stirred at rt in methanol under Ar, and Pd/C (5 mol% of Pd) was added under Ar-flow. Ar was replaced with H_2 and resulting heterogeneous mixture was stirred for 2h. Mixture was then filtered trough short pad of celite and solvents were evaporated to give hydrogenated product as clear oil (99%).
12. Diastereoselectivities of hydrogenations were determined by GC, ^{1}HNMR or HPLC. Proof of stereochemistry was obtained by converting **15** to known compound **18** and its spectra was examined (ref. 2).



15 **18**

13. Interestingly, hydrogenation of L-serine derived didehydroamino acid derivative with Pd/C in *i*-propanol proceeded with excellent selectivity (96:4). Avenoza, A.; Cativiela, C.; Peregrina, J.M.; Zurbano, M.M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555.
14. a) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, **1979**. b) Rylander, P.N. *Hydrogenation Methods,* Academic Press: New York, **1985**. c) Siegel, S. in *'Comprehensive Organic Synthesis'*, ed. Trost, B.M. Pergamon, **1991**, vol 8, chapter 3.1.
15. a) The order of decreasing activity to promote isomerization is Pd>> Rh, Ru, Pt > Ir, Nishimura, S.; Sakamoto, H.; Ozawa, T. *Chem. Lett.* **1973**, 855. b) Brown, R., Kemball, C., Sadler, I.H. *Proc. R. Soc. London A*, **1989**, *424*, 39. c) In our hands no hydrogenation occurred with Ir/C on experiments with either **8** or **9**.

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