Pergamon

Tetrahedron Letters, Vol. 36, No. 42, pp. 7619-7622, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01584-1

Highly Diastereoselective Diels–Alder Reaction Mediated by a Chiral Auxiliary Derived from Amino Indanol: The Role of Conformation on Diastereoselectivity.

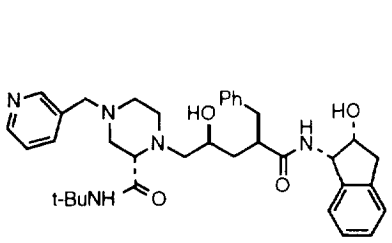
Ian W. Davies*, Chris H. Senanayake, Laurie Castonguay‡, Robert D. Larsen, Thomas R. Verhoeven and Paul J. Reider.

Department of Process Research and ‡Department of Molecular Design and Diversity, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065.

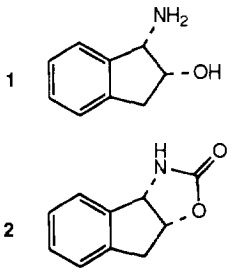
Summary: The oxazolidinone **2** *derived from amino indanol* **1** *functions as a very efficient chiral auxiliary for the Diels–Alder reaction. The effect of conformation has been explored using a range of constrained phenyl glycinol analogues.*

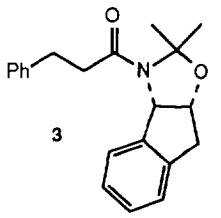
The orally active HIV protease inhibitor *Indinavir* (L-735,524) is one of a group of compounds that are in advanced clinical trials for the treatment of AIDS.[1] This class of compounds contains the *1S,2R*-1-amino indan-2-ol skeleton **1**. We have recently disclosed a highly efficient enantioselective synthesis of **1** from indene *via* indene oxide using a Ritter reaction.[2] In this communication we wish to report the use of oxazolidinone **2** derived from **1** as an efficient chiral auxiliary for the Diels–Alder reaction.

The synthesis of *Indinavir* relies on the diastereoselective alkylation of the (*Z*)-lithium amide of **3** with >95% d.e.[3] Imides derived from **3** have also been shown to undergo face selective alkylation and aldol reactions.[4] On the basis of these observations, we reasoned that the amino indanol platform should control the outcome of other processes that require face selectivity, for example, the Diels–Alder reaction.



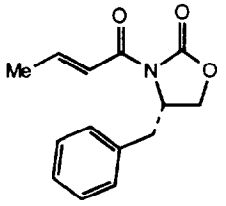
Indinavir



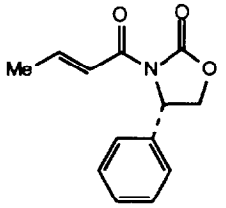


Pioneering work in this area was performed by Evans using oxazolidinones derived from amino alcohols as chiral auxiliaries.[5] Evans was able to demonstrate that very high levels of selectivity were accessible in the Diels–Alder reaction of isoprene using the oxazolidinone **4** (88% d.e.) but much lower levels of selectivity were apparent with **5** (35% d.e.). We reasoned that the low level of selectivity obtained with **5** was due to the rotationally labile phenyl ring – that can be less or more sterically demanding depending on its conformation. Amino indanol **1**

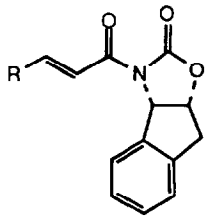
is a conformationally constrained analog of phenyl glycinol and as such may provide higher levels of stereocontrol in the Diels–Alder reaction.



4



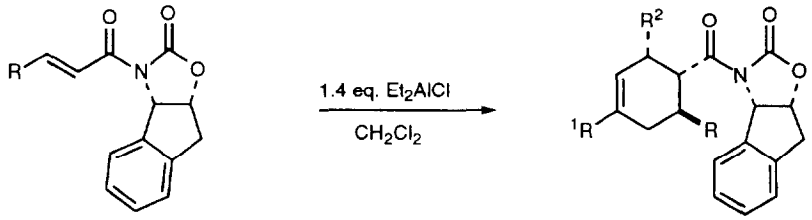
5



6, R = H
7, R = Me

To test our hypothesis we prepared the oxazolidinone **2** from amino indanol **1** using triphosgene (96%). From this intermediate the acrylimide **6** and crotonimide **7** dienophiles were prepared through slight modification of the conditions recently described by Ho and Mathre (LiBr, ethylacetate, triethylamine, acid anhydride).[6]

Following the conditions described by Evans the dienophiles **6** and **7** were reacted with isoprene and piperylene in the presence of 1.4 equivalents of Et_2AlCl. Table 1 summarizes the results from these studies. In all cases examined, the reaction proceeded with good to excellent levels of diastereo- and *endo* -selectivity. The stereocontrol observed in the reaction of imide **7** (entry 3, 93.4% d.e.) is in complete contrast to the low levels of stereocontrol exhibited by **5** (35% d.e.). It was also gratifying to observe that the amino indanol oxazolidinone provided enhanced levels of stereocontrol – even at higher temperatures – than those reported for the oxazolidinone **4**.

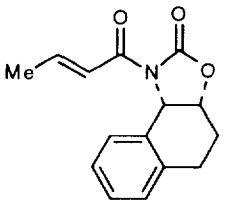


6, **7** **8a**, **8b**, **9a**, **9b**

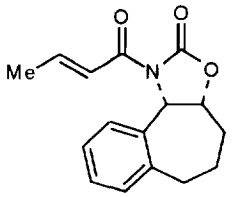
entry	dienophile	diene	product	temp °C	%d.e.	*endo:exo*	%yield
1	**6**, R = H	isoprene	**8a**, R = H, R^1 = Me, R^2 = H	-70	87.5	-	85
2	**6**, R = H	piperylene	**8b**, R = H, R^1 = H, R^2 = Me	-70	98.4	50:1	69
3	**7**, R = Me	isoprene	**9a**, R = Me, R^1 = Me, R^2 = H	-35	93.4	-	n.d.
4	**7**, R = Me	isoprene	**9a**, R = Me, R^1 = Me, R^2 = H	-15	92.9	-	88
5	**7**, R = Me	piperylene	**9b**, R = Me, R^1 = Me, R^2 = Me	-35	98.4	30:1	n.d.
6	**7**, R = Me	piperylene	**9b**, R = Me, R^1 = Me, R^2 = Me	-15	93.7	25:1	77

Table 1: Diels–Alder reaction using 1.8M Et_2AlCl in toluene; n.d. – yield not determined; % d.e. determined by HPLC comparison of the crude reaction mixture with authentic samples. The products were purified on silica gel using 20% ethyl acetate in hexane as eluent; *endo* selectivity was confirmed by nOe studies.

To verify that amino indanol **1** was behaving as a conformationally restricted phenyl glycinol equivalent, we prepared the homologous six- and seven-membered ring-containing systems **10** and **11** from the appropriate amino alcohols.[7] Upon subjection to the standard reaction conditions each dienophile gave low levels of stereocontrol (30-35% d.e.). These results compare directly to the unconstrained phenyl glycinol oxazolidinone **5** (35% d.e.). Hence the single methylene link in the aminoindanol residue plays a unique role in providing high levels of diastereocontrol in the Diels–Alder reaction.

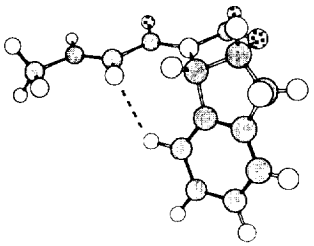


10

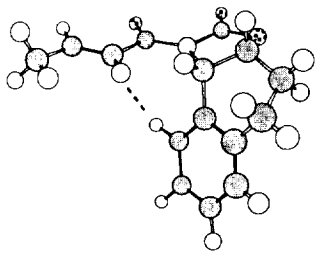


11

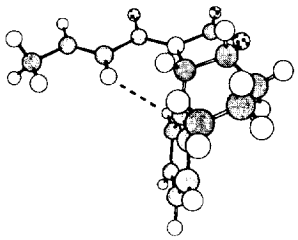
Conformations available to the oxazolidinones **5**, **7**, **10**, and **11** were examined by computational methods.[8] Conformations of the dienophiles were generated using distance geometry and were energy minimized. To mimic the tetrahedral aluminum adduct, the imide carbonyls were held in a *cis*-coplanar geometry during conformer generation. The resulting low energy conformations clearly demonstrate that the six- and seven-membered rings **10** and **11** are conformationally flexible, whereas the amino indanol **7** is essentially rigid. The amino indanol platform shields the bottom face of the dienophile most effectively as the C_{ortho}–H resides underneath the C_α of the crotonimide. The shielding of the bottom face of the dienophile **7** is clearly evident upon comparing C_{ortho}–H – C_α–H distances in the minimized structures; **7**, 2.6Å; **10**, 2.8Å; **11**, 3.3Å; **5**, 3.0Å.



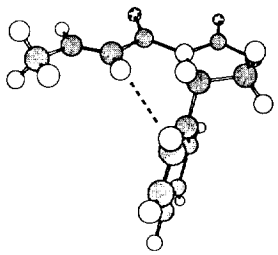
7



10

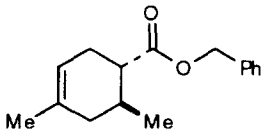


11

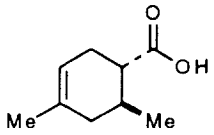


5

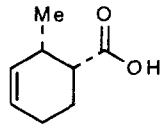
Finally, to demonstrate the synthetic utility of amino indanol as a chiral auxiliary we have examined the cleavage under standard conditions.[5] Treatment of the purified adduct **9a** with lithium benzyl oxide gave the desired ester (+)-**12** in 86% yield and >99% e.e. as determined by G.C.[9] The hydrolysis of **9a** with LiOOH gave (+)-**13**; **8b** gave (+)-**14** in >99% e.e. and 90% yield with >92% recovery of the oxazolidinone **3**. These results not only serve to confirm the absolute configuration, but also demonstrate that the oxazolidinone derived from amino indanol is an excellent addition to the family of Evans auxiliaries.



(+)-12



(+)-13



(+)-14

In conclusion we have demonstrated that aminoindanol is a useful, readily cleaved chiral auxiliary for the Diels–Alder reaction with up to 98.4% d.e. being accessible in the cycloaddition reaction. We are currently investigating the use of chiral ligands based on the amino indanol platform and these results will be reported in due course.

References

1. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J; Quintero, J. C.; Blahy, O. M.; Roth, E; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I. -W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096.
2. Senanayake, C.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Letters*, **1995**, *36*, 3993.
3. Maligres, P. E.; Upadhyay, V.; Rossen, K.; Ciancosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Letters*, **1995**, *36*, 2195.
4. Ghosh, A. K.; Duong, T. T.; Mckee, S. P. *J. Chem. Soc., Chem. Commun.*, **1992**, 1673.
5. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.*, **1988**, *110*, 1238; Evans, D. A.; Chapman, K. T.; Bisaha, *Tetrahedron Letters*, **1984**, *25*, 4071; Evans, D. A.; Chapman, K. T.; Hung, D. T., Kawaguchi, A.; Bisaha, J. *Angew. Chem., Int., Ed., Engl.*, **1987**, *26*, 1184.
6. Ho, G. -J.; Mathre, D. *J. Org. Chem.*, **1995**, *60*, 2271.
7. Senanayake, C.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Preceding paper in this issue.*
8. 500 conformations (the two carbonyls held *cis*-coplanar) were generated for dienophiles **5, 7, 10**, and **11** using an in-house distance geometry program, JG (Kearsley, *unpublished results*). All resulting conformations were energy minimized using a distance-dependent dielectric constant and the MMFF94s forcefield (Halgren, *J. Comp. Chem.*, **1995**, 0000) implemented in the molecular mechanics program, OPTIMOL (Holloway et al., *J. Med. Chem.*, **1995**, *38*, 305). All low energy conformations (within 3 kcals of the minimum energy) were compared. Queries regarding the calculations should be directed to Dr. Laurie Castonguay.
9. G.C. was performed with a HP 5890 instrument using an FID (injector 250°C, detector 250°C) on an Astec BPA column (30m x 0.25mm, head pressure 12 psi) at 140°C for acids and 190°C for esters. (+)-**12** $[\alpha]_D$ +171 (c=1.0, CH_2Cl_2), lit.[5] $[\alpha]_D$ +55 (c = 0.055, CH_2Cl_2), R_t (+) 20.39 min, (-) 22.26 min; (+)-**13** $[\alpha]_D$ +49 (c=1.0, CH_2Cl_2), R_t (+) 19.93 min, (-) 20.40 min; (+)-**14** $[\alpha]_D$ +277 (c=2.15 , CH_2Cl_2), R_t (+) 22.45 min, (-) 20.70 min.

(*Received in USA* 20 *July* 1995; *revised* 14 *August* 1995; *accepted* 17 *August* 1995)