Tetrahedron Letters,Vol.24,No.42,pp 4535-4538,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

AUXILIARY-REAGENT MEDIATED ASYMMETRIC INDUCTION IN THE AZA-CLAISEN REARRANGEMENT

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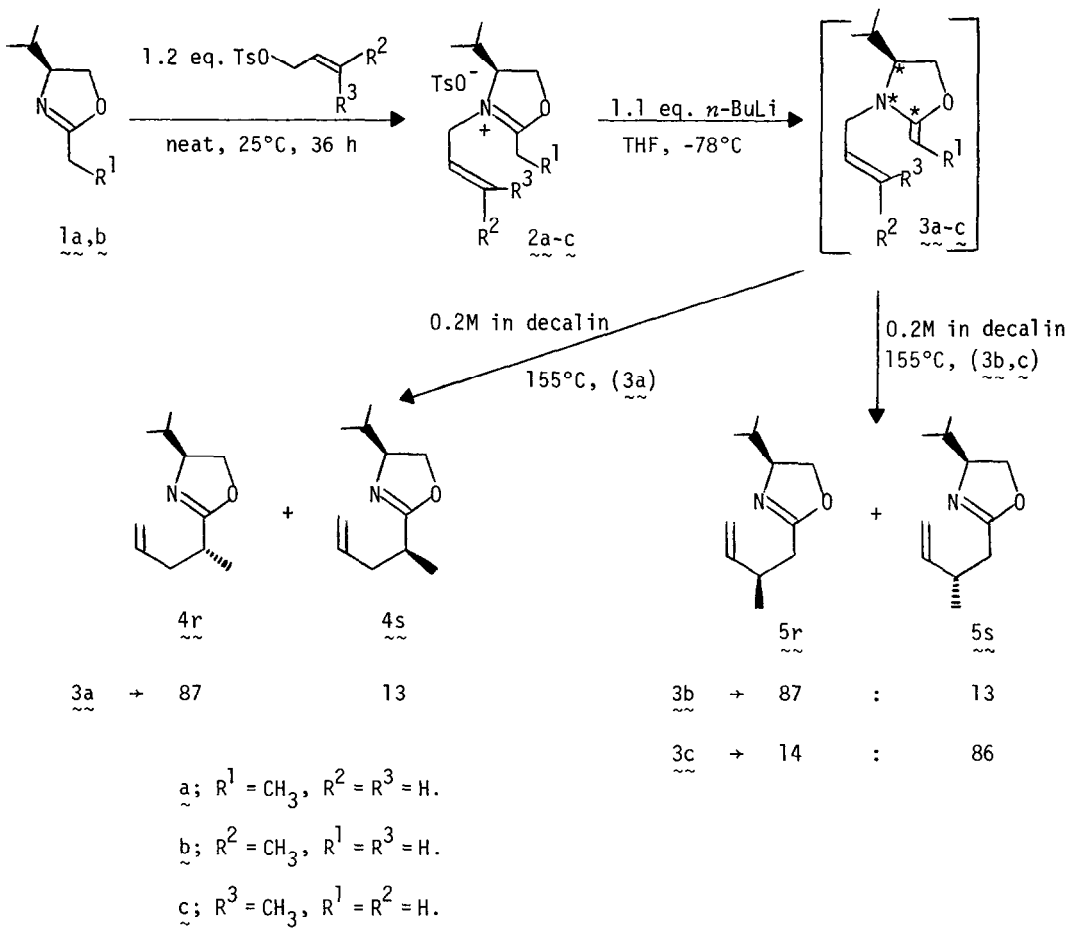
Summary: Chiral induction (72-74% diastereomeric excess) in an auxiliary-reagent mediated aza-Claisen rearrangement yielding 2- and 3-methylpent-4-enoic acids has been demonstrated.

Claisen rearrangements ([3,3] sigmatropic reorganization of allyl vinyl hetero-systems) have been employed in numerous aspects of organic synthesis over the past 15 years.[1] The foundation for this utility lies in the stereo-differentiating ability of these concerted rearrangements. Application of this intrinsic selectivity to asymmetric induction *via* chirality transfer, termed "self-immolative" asymmetric induction,[2] has been demonstrated in several elegant synthetic studies. Representative examples include the Stork-Raucher[3] synthesis of (+)-15(*S*)-PGA_2 from *L*-erythrose *via* the normal Claisen rearrangement and the Hill-Khatri[4] synthetic approach to polyzonimine pheremones from (*S*)-(-)-*N*-phenyl-α-methallylamine *via* the aza-Claisen rearrangement. However, the self-immolative Claisen rearrangement has several important drawbacks. These include the required preparation of an optically pure allylic substrate and the inherent sacrifice of the initial chiral center. These limitations, plus the fundamental importance of enantioselective methods for C,C-bond formation,[5] have prompted us to investigate the feasibility of auxiliary reagent mediated asymmetric Claisen rearrangements.[6]

We reasoned that an auxiliary chiral center covalently bound to nitrogen would create a transition state bias in the aza-Claisen rearrangement. To maximize the topological effect of the auxiliary chiral center, this center, the nitrogen atom, and C_1 of the vinyl moiety (*atoms in 3) are confined within a five-membered ring. Herein we report our preliminary results delineating the preparation of *N*-allylketene *N*,*O*-acetals (3) from amino acids, their diastereoface selective reorganization to 2-(3-butenyl)oxazolines (4 or 5), and the subsequent hydrolysis of these oxazolines to optically active pent-4-enoic acid derivatives.

Oxazolines 1a,b[7a] were prepared under standard conditions[8] by condensing *L*-valinol[9] with the appropriate imidate hydrochlorides. Treatment of oxazoline 1b with allyl chloride or bromide under a wide variety of reaction conditions resulted in only low yields of the desired oxazolinium salts. However, *N*-allylation with the appropriate allylic tosylate provided the desired salts 2a-c[7a] in > 98% yield. Subsequent neutralization of these oxazolinium salts afforded *N*-allylketene *N*,*O*-acetals 3a-c which were rearranged without isolation.[10] This two pot sequence afforded oxazolines 4[7a,b] or 5[7a,b] in excellent isolated yields (1 → 4 or 5 in > 85% overall yield).

Scheme



The diastereoface selectivities of these aza-Claisen rearrangements were determined as follows. Oxazoline 4 was hydrolysed under standard conditions (3N HCl, 90°C, 90 min)[8] and subsequent chiroptic measurements on the purified acid established that (*R*)-(-)-2-methylpent-4-enoic acid[11] was formed in excess. Thus, *N*,*O*-acetal 3a rearranged preferen-

tially to oxazoline 4r. Similarly, (*E*)-3b afforded 5r in excess as evidenced by hydrolysis of 5 to (*R*)-(-)-3-methylpent-4-enoic acid.[12] In contrast, (*Z*)-3c gave a preponderance of oxazoline 5s. The diastereomer ratios of rearranged oxazolines 4r/4s and 5r/5s (see *Scheme*) were established by HPLC analysis.[13] While ^{1}H NMR analysis of oxazolines 4 or 5 did not cleanly differentiate diastereomers, their conversion to the corresponding *N*-methyloxazolinium salts (1.0 eq. 4 or 5, 2.0 eq. dimethyl sulfate, neat, room temperature, 3 hrs; diethyl ether trituration; > 90% yield) and subsequent ^{1}H NMR analysis[14] at 500-MHz confirmed a 72-74% d.e. (diastereomeric excess) for 3a→4r, 3b→5r, and 3c→5s.

Control experiments indicate that the diastereoface selectivity of this aza-Claisen rearrangement is in fact greater than 87:13. For example, ^{1}H NMR examination of oxazolinium salts 2b and 2c indicated cross-contamination to the extent of 4% 2c in 2b and 7% 2b in 2c. Hence the corrected face selectivity is ca. 90:10, a diastereomeric excess of 80%. Ketene *N*,*O*-acetal 3a, prepared by *n*-BuLi/THF/-78°C neutralization of 2a, was isolated[15] by concentration at 2 torr followed by trituration with either chloroform-*d* or benzene-d_6. Subsequent ^{1}H NMR analysis revealed only one vinylic methyl resonance [($CDCl_3$) δ 1.57 (d, 3H, J = 7Hz); (C_6D_6) δ 2.00 (d, 3H, J = 7Hz)]. Heating 3a for 30 min at 120°C in benzene-d_6 caused no detectable *E*/*Z*-*N*,*O*-acetal isomerization suggesting that 3a is > 95% the *Z*-*N*,*O*-acetal.

In each of the examples investigated, the absolute configuration at the new chiral center is that predicted by approach of the allyl moiety to the vinyl moiety from the face opposite the 4-isopropyl group (see *Scheme*). This observation implies significant sp^3-character at nitrogen in the transition state. The observed face selectivity is then both a consequence of transition state interconversion via nitrogen inversion (3-allyl and 4-isopropyl moieties *syn* ⇌ 3-allyl and 4-isopropyl moieties *anti*) and of preferential rearrangement through the less congested conformation.

Acknowledgment

The 500-MHz NMR measurements were made by Mr. D. H. Burns. Acknowledgment is made to the Committee on Research of the University of California, Davis and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We gratefully acknowledge IBM Instruments for donation of an LC/9533 Ternary High-pressure Liquid Chromatography system.

References

1. Reviews: (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* 1975, 22, 1; (b) Ziegler, F. E. *Acc. Chem. Res.* 1977, 10, 227; (c) Bennett, G. B. *Synthesis* 1977, 589; (d) Murray, A. W. *Org. Reaction Mech.* 1980, Chap. 14, pp 517-536.
2. Mislow, K. "Introduction to Stereochemistry"; Benjamin: New York, 1965; p 131.
3. Stork, G.; Raucher, S. *J. Am. Chem. Soc.* 1976, 98, 1583.
4. Hill, R. K.; Khatri, H. N. *Tetrahedron Lett.* 1978, 4337.
5. (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* 1978, 10, 175; (b) Valentine, Jr., D.; Scott, J. W. *Synthesis* 1978, 329; (c) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* 1979, 35, 2797.
6. The concept of auxiliary reagent induced asymmetric Claisen rearrangement has received little attention. See: Oda, J.; Igarishi, T.; Inouye, Y. *Bull. Inst. Chem. Res. Kyoto Univ.* 1976, 54, 180; C. A. 1977, 86, 88836m.
7. (a) The spectroscopic properties (IR, NMR, and mass spectrum) of this compound were entirely consistent with the assigned structure; (b) A satisfactory combustion analysis (± 0.3% for C, H, and N) was obtained for this compound.
8. Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* 1976, 98, 567.
9. Chiral shift studies on 1b indicated none of the *R*-antipode [1b 0.26 M in $CDCl_3$, 0.18 eq. $Eu(hfc)_3$: (*R*)-1b δ 1.81 (d, 3H, J = 7Hz), 1.72 (d, 3H, J = 7Hz); (*S*)-1b δ 2.17 (d, 3H, J = 7Hz), 2.02 (d, 3H, J = 7Hz)] verifying that *L*-valinol was > 95% optically pure.
10. Ireland, R.; Willard, A. *J. Org. Chem.* 1974, 39, 421.
11. Klyne, W.; Buckingham, J. "Atlas of Stereochemistry"; 2nd Ed., Vol. 1; Chapman and Hall Ltd.: London, 1978; p 38.
12. Personal communication with Professor G. McGarvey, University of Virginia.
13. High-pressure liquid chromatography separation of these diastereomers was accomplished on a silica column using a 10% ethyl acetate:90% *n*-hexane solvent system (retention times in minutes of 4r:4s::18.8:20.4 and 5r:5s::26.6:28.2).
14. These *N*-methyloxazolinium salts gave baseline resolved methyl resonances for the diastereomeric methyl substituted 2-(3-butenyl) moieties [500-MHz, $CDCl_3$: 4r *N*-methyl salt, δ 1.44 (d, 3H, J = 7Hz); 4s *N*-methyl salt, δ 1.26 (d, 3H, J = 7Hz); 5r *N*-methyl salt, δ 1.13 (d, 3H, J = 7Hz); 5s *N*-methyl salt, δ 1.17 (d, 3H, J = 7Hz)].
15. For the isolation of oxazine derived *N,O*-acetals see: (a) Meyers, A. I.; Nazarenko, N. *J. Am. Chem. Soc.* 1972, 94, 3243; (b) Meyers, A. I., Nazarenko, N. *J. Org. Chem.* 1973, 38, 175.

(Received in USA 5 July 1983)