Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1841-1844, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00165-2

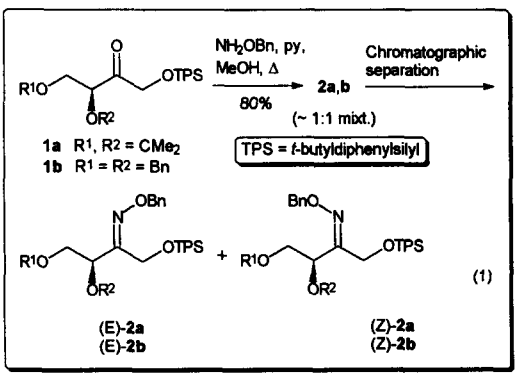
Diastereoselective Additions of Organolithium Reagents to the C=N Bond of Protected Erythrulose Oxime Ethers. Synthesis of Enantiopure α,α-Disubstituted α-Aminoacids

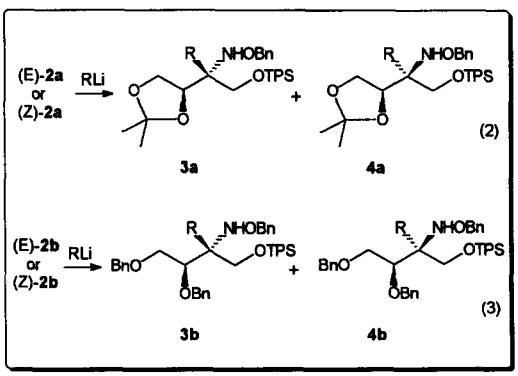
J. Alberto Marco,*[a] Miguel Carda,*[b] Juan Murga,[b] Florenci González,[b] and Eva Falomir[b]

[a]*Depart. de Q. Orgánica, Univ. de Valencia, E-46100 Burjassot, Valencia, Spain.*
[b]*Depart. de Q. Inorgánica y Orgánica, Univ. Jaume I, Castellón, E-12080 Castellón, Spain.*

Abstract: The addition of organolithium reagents to the C=N bond of several erythrulose-derived chiral (E)- and (Z)-ketoxime ethers has been shown to be highly diastereoselective for the (E)-isomers. A chelated transition state has been proposed to explain this result. The addition products were converted into the two α,α-disubstituted α-aminoacids (R)-2-(—)-methylserine and .(R)-(+)-2-phenylserine.

The addition of carbon nucleophiles to C=N bonds[1] is a synthetically important method of preparing various types of compounds of biological importance such as aminopolyols[2] and non-proteinaceous aminoacids.[3] The latter are very useful both as enzyme inhibitors and for the synthesis of peptidomimetics.[4] Among them, α,α-disubstituted α-aminoacids, which contain a nitrogen atom bound to a quaternary carbon, have attracted a particular interest.[5] There are few methods of preparing such compounds in enantiopure form. Most of them rely on alkylation of glycine enolate anion equivalents.[3,5] This fact puts some limits to their applicability, as certain α-aminoacids such as those with α-*tert*-alkyl or α-aryl substituents cannot be easily prepared in this way. We herein report that the addition of organolithium reagents to chiral ketoxime ethers (E)- and (Z)-**2a/2b** takes place with often high stereocontrol to yield the differentially protected aminopolyols **3/4** (eqs 1-3). These aminoalcohols can be converted into enantiopure α,α-disubstituted α-aminoacids, including those not easily available by previous methodologies.





There are few reports on diastereoselective additions to the C=N bond of chiral ketone imino derivatives, and most of them refer to reduction processes.[6] In contrast, the diastereoselective additions of *carbon* nucleophiles has been investigated only in a very limited number of cases.[7-9] We have previously reported on the

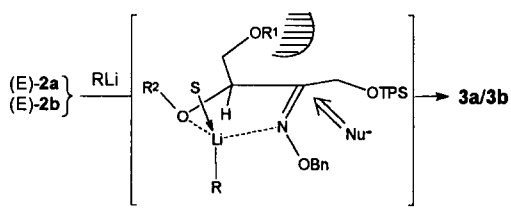
diastereoselective addition of organometallic reagents to the C=O bond of O-protected L-erythrulose derivatives **1a/1b**.[10] Through reaction with O-benzyl hydroxylamine, these compounds were converted into E/Z mixtures of the corresponding ketoxime ethers **2a/2b**, which were then separated into pure geometrical isomers by column chromatography (eq 1). These oximes were at least 98% optically pure, as confirmed by NMR analysis of Mosher derivatives (MTPA residue instead of TPS). Either of the stereoisomers of **2a/2b** was then subjected to reaction with various organometallic reagents (eqs 2-3). The results are presented in Table 1.

Table 1. Stereoisomer Distribution in the Addition of Organolithium Reagents to Chiral Oximes **2a/2b**.[a]

Entry	Oxime	RLi	T[b]	Yield[c]	**3 / 4**[d]
1	(E)-**2a**	MeLi	0	91	93 : 7
2	(E)-**2b**	MeLi	0	71	>95 : 5
3	(Z)-**2a**	MeLi	0	62	25 : 75
4	(Z)-**2b**	MeLi	0	41	23 : 77
5	(E)-**2a**	*n*BuLi	—78	73	93 : 7
6	(E)-**2b**	*n*BuLi	—78	95	>95 : 5
7	(Z)-**2a**	*n*BuLi	0	42	30 : 70
8	(Z)-**2b**	*n*BuLi	0	Dec.[e]	
9	(E)-**2a**	*t*BuLi	—78	60	>95 : 5
10	(E)-**2b**	*t*BuLi	—78	Dec.	
11	(Z)-**2a**	*t*BuLi	0	Dec.[e]	
12	(Z)-**2b**	*t*BuLi	0	Dec.[e]	
13	(E)-**2a**	PhLi	—78	70	>95 : 5
14	(E)-**2b**	PhLi	—78	85	>95 : 5
15	(Z)-**2a**	PhLi	0	68	75 : 25
16	(Z)-**2b**	PhLi	0	70	68 : 32
17	(E)-**2a**	allylLi	—78	73	80 : 20
18	(E)-**2b**	allylLi	—78	50	>95 : 5
19	(Z)-**2a**	allylLi	—78	61	33 : 67
20	(Z)-**2b**	allylLi	—78	50	13 : 87

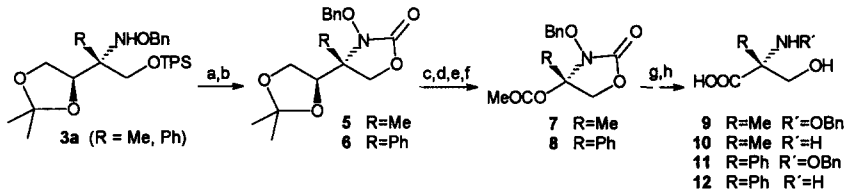
[a]All reactions were performed in Et_2O. The reaction time was 1 hour in all cases, although some of the reactions, mostly those of the (E) isomers, were complete in less than 15 min. [b]In degrees (°C). [c]Overall yield (%) of both stereoisomers. [d]Determined by $^1H/^{13}C$ NMR. [e]At lower temperatures, a partial recovery of the starting material was the only result.

The relatively hindered ketoximes **2a/2b** were not very reactive. Only organolithium derivatives were able to add to the C=N bond with subsequent formation of various N-*tert*-alkyl O-benzyl hydroxyl amines **3/4**. The reactions were in general quite diastereoselective, most particularly in the case of the (E) isomers, where the minor diastereoisomer was in most cases not detectable by NMR spectroscopy. In fact, the (E) isomers proved both more reactive and more diastereoselective than their (Z) counterparts. This may be due to the formation of a five-membered α-chelate (see below) involving the lithium, nitrogen and oxygen atoms of the α-OR group.[1d,7,11] This allows the prediction of a preferred approach from the less hindered *si* side of the C=N bond and the predominant formation of aminopolyols **3a/3b**, in line with observations. Most likely, the (Z) isomers react through a non-cyclic transition state of the Felkin-Anh type,[1d,12] which leads predominantly to the opposite stereoisomers **4a/4b**.[13,14]



As an example of the synthetic potential of the aforementioned products, we have prepared the aminoacids (R)-(—)-2-methylserine **10** and (R)-(+)-2-phenylserine **12** in optically pure form. Desilylation of **3a** (R=Me or Ph) followed by treatment with carbonyldiimidazole, gave rise to oxazolidinones **5** and **6**, respectively, in 85% overall yield. Acetonide cleavage, two-step oxidation of the diol moiety and

esterification of the crude acid yielded **7** and **8** (40% overall yield for the four steps), which were then hydrolized under basic conditions. This afforded the corresponding N-benzyloxy aminoacids **9** and **11**, hydrogenolysis of which furnished, respectively, (R)-(—)-2-methylserine **10**, mp 248-250° (dec.), $[\alpha]_D$ –6.3 (H_2O, c 1.1), and (R)-(+)-2-phenylserine **12**, mp 225-230° (dec.), $[\alpha]_D$ +19.5 (H_2O, c 0.3), in 50% yield from **7** and **8**. The physical data and optical rotation of synthetic **10** were identical to those reported in the literature.[5b,5d,15] The aminoacid 2-phenylserine has previously been described only in racemic form,[16] although a derivative with unknown configuration was obtained in 67% ee via a metal-catalyzed process.[17]



Reaction conditions. a) TBAF, THF, RT. b) CDI, C_6H_6, Δ (85% overall). c) $(CH_2SH)_2$, TsOH, $CHCl_3$, Δ. d) $NaIO_4$, aq THF. e) $NaClO_2$, aq *t*BuOH. f) CH_2N_2 (40% overall). g) aq NaOH/EtOH, RT. h) H_2, Pd/C, MeOH (50% overall).

The methodology we describe in this communication is therefore very useful for the preparation of many types of α,α-disubstituted α-aminoacids. Furthermore, intermediates **3/4** carry several hydroxyl groups, a fact which opens the way to the synthesis of other biologically relevant, polyfunctionalized compounds, such as polyhydroxylated aminoacids,[18] diaminoacids,[19] N-hydroxy aminoacids,[20] branched aminosugars,[21] etc. Finally, since D-erythrulose derivatives enantiomeric to **1a/1b** are also easily available,[10a,22,23] all the aforementioned compounds can be prepared in either antipodal form. Efforts in these directions are now in progress.

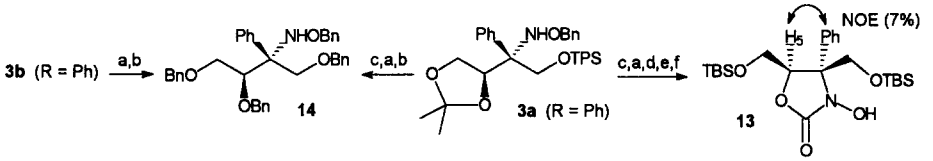
Acknowledgements - This research has been financially supported by the Spanish Ministry of Education and Science (DGICYT projects PB92-0745 and PB95-1089) and by BANCAJA (project B-10-CE). E.F. thanks the Conselleria de Educaciò de la Generalitat Valenciana for a pre-doctoral fellowship.

REFERENCES AND NOTES

1. (a) Harada, K. in *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; John Wiley and Sons: New York, 1970; Chapt. 6, pp 255-298. (b) Tennant, G. in *Comprehensive Organic Chemistry*; Barton, D.H.R., Ollis, W.D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, pp 385-590. (c) Yamaguchi, M. in *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 325-353. (d) Volkmann, R.A. in *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 355-396.
2. See leading references in: Jäger, V.; Hümmer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769-776.
3. (a) Williams, R.M. *Synthesis of Optically Active α-Aminoacids*; Pergamon Press: Oxford, 1989. (b) Williams, R.M.; Hendrix, J.A. *Chem.Rev.* **1992**, *92*, 889-917. (c) Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539-1650.
4. Gante, J. *Angew.Chem.Int.Ed.Engl.* **1994**, *33*, 1699-1720.
5. For some recent references on α,α-disubstituted α-aminoacids, see: (a) Williams, R.M.; Im, M.-N. *J.Am.Chem.Soc.* **1991**, *113*, 9276-9286. (b) Colson, P.J.; Hegedus, L.S. *J.Org.Chem.* **1993**, *58*, 5918-5924. (c) Toniolo, C.; Formaggio, F.; Crisma, M.; Valle, G.; Boesten, W.H.J.; Schoemaker, H.E.; Kamphuis, J.; Temussi, P.A.; Becker, E.L.; Précigoux, G. *Tetrahedron* **1993**, *49*, 3641-3653. (d) Moon, S.-H.; Ohfune, Y. *J.Am.Chem.Soc.* **1994**, *116*, 7405-7406. (e) Ojima, I. *Acc.Chem.Res.* **1995**, *28*, 383-389.
6. See, for example: (a) Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* **1994**, 5389-5392. (b) Moss, N.; Gauthier, J.; Ferland, J.-M. *Synlett* **1995**, 142-144. (c) Harada, K.; Shiono, S. *Bull.Chem.Soc.Jpn.*

1984, *57*, 1040-1045. (e) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull.Chem.Soc.Jpn.* **1986**, *59*, 525-533. (f) Iida, H.; Yamazaki, N.; Kibayashi, C. *J.Chem.Soc.Chem.Commun.* **1987**, 746-748. (g) Williams, D.R.; Osterhout, M.H. *J.Am.Chem.Soc.* **1992**, *114*, 8750-8751. (h) Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* **1993**, 3271-3274. (i) Zhu, Q.-C.; Hutchins, R.O. *Org.Prep.Proc.Int.* **1994**, *26*, 193-236.

7. Addition of allyl-type organometallics: Yamamoto, Y.; Asao, N. *Chem.Rev.* **1993**. *93*, 2207-2293.
8. Diastereoselective addition of a *chiral* sulfoxide anion to an *achiral* ketimine: Bravo, P.; Capelli, S.; Meille, S.V.; Viani, F.; Zanda, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2009-2018.
9. For a stereoselective Strecker-type synthesis with a ketimine, see ref. 5d.
10. (a) Carda, M.; González, F.; Rodríguez, S.; Marco, J.A. *Tetrahedron: Asymmetry* **1992**, *3*, 1511-1514. (b) Carda, M.; González, F.; Rodríguez, S.; Marco, J.A. *Tetrahedron: Asymmetry* **1993**, *4*, 1799-1802. (c) González, F. Ph.D. Thesis, Univ. Jaume I, 1995.
11. Reetz, M.T. *Acc.Chem.Res.* **1993**, *26*, 462-468.
12. (a) Anh, N.T. *Top.Curr.Chem.* **1980**, *88*, 145-162. (b) Eliel, E.L. in *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapt. 5, pp. 125-155.
13. The configurational assignments of the C=N bond in oxime ethers were based on NMR data,[14] including NOE measurements. The configuration of the new stereogenic center in stereoisomers **3a/3b** was established as illustrated below with the example of **3a** (R = Ph), which was converted into oxazolidinone **13** (TBS = *t*-butyldimethylsilyl). In this compound, a clear NOE was observed between H-5 (heterocycle numbering) and the *ortho*-aromatic protons of the phenyl ring. The configuration of **3b** (R = Ph) was established by conversion into the perbenzylated derivative **14**, which proved identical to the compound obtained from **3a** as indicated below. The configurations of the stereoisomers **3a/3b** with R = Me, *n*Bu, *t*Bu and allyl were established through essentially analogous sequences of reactions and observation of NOEs of similar type.



Reaction conditions. a) TBAF, THF, RT. b) NaH, THF, BnBr. c) PPTS aq MeOH, Δ. d) TBSCl, imidazole, RT. e) Triphosgene, Et_3N, CH_2Cl_2, RT. f) H_2, Pd/C, MeOH.

14. (a) Karabatsos, G.J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079-1095. (b) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: Weinheim, 1987; Chapt. 4, pp 240-242.
15. Seebach, D.; Aebi, J.D.; Gander-Coquoz, M.; Naef, R. *Helv.Chim.Acta* **1987**, *70*, 1194-1216.
16. Henze, H.R.; Craig, W.C. *J.Org.Chem.* **1945**, *10*, 2-9.
17. Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, 235-238.
18. For recent references, see: (a) Palomo, C.; Aizpurua, J.M.; Cabré, F.; García, J.M.; Odriozola, J.M. *Tetrahedron Lett.* **1994**, 2721-2724. (b) Schmeck, C.; Hegedus, L.S. *J.Am.Chem.Soc.* **1994**, *116*, 9927-9934.
19. For recent references, see: (a) Palomo, C.; Aizpurua, J.M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J.M. *Tetrahedron Lett.* **1994**, 2725-2728. (b) Reetz, M.T.; Röhrig, D.; Harms, K.; Frenking, G. *Tetrahedron Lett.* **1994**, 8765-8768.
20. Kolasa, T.; Sharma, S.K.; Miller, M.J. *Tetrahedron* **1988**, *44*, 5431-5440.
21. For a recent reference, see: Greven, R.; Jütten, P.; Scharf, H.-D. *J.Org.Chem.* **1993**, *58*, 3742-3747.
22. Marco, J.A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann.Chem.* **1996**, 1801-1810.
23. Murga, J., Ph.D. Thesis, Universitat Jaume I, 1996.

(*Received in UK* 8 *January* 1997; *accepted* 24 *January* 1997)