Pergamon

Tetrahedron Letters 40 (1999) 2887–2890

TETRAHEDRON LETTERS

Stereoselective Elaboration of Side Chain Residues in Cyclopropane-Containing Dipeptide Isosteres

Stephen F. Martin* and Roy K. Hom

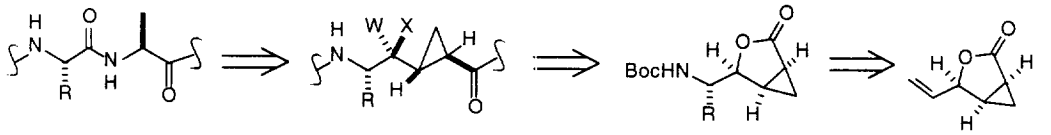
Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712 USA

Received 12 January 1999; revised 15 February 1999; accepted 16 February 1999

Abstract. A variety of alkyl, substituted alkyl, and aryl side chain residues in cyclopropane-containing dipeptide isosteres were introduced by the highly diastereoselective (dr ≥20:1) additions of organolithium or Grignard reagents to *N*, *N*-dimethylhydrazone **6**. The resulting hydrazines were transformed into the corresponding *N*-Boc-protected amines with little or no stereochemical erosion.

In the context of a general program directed toward the design and synthesis of novel peptide mimics, we introduced substituted cyclopropanes **2** as replacements of the Xaa-Ala dipeptide array **1**. The efficacy of such mimics was established by the preparation of potent inhibitors of renin and HIV protease containing truncated dipeptide replacements related to **2**.[1] An integral component of our efforts in this area has been the development of methods for the asymmetric synthesis of functionalized cyclopropanes via the enantioselective, rhodium-catalyzed cyclizations of allylic diazoacetates.[2] In this report, we describe an efficient method for elaborating the vinyl side chain in the cyclopropyl lactone **4** into the lactones **3**, which can then be transformed into the Xaaψ[COcp]Ala replacements **2** (Scheme 1).

Scheme 1



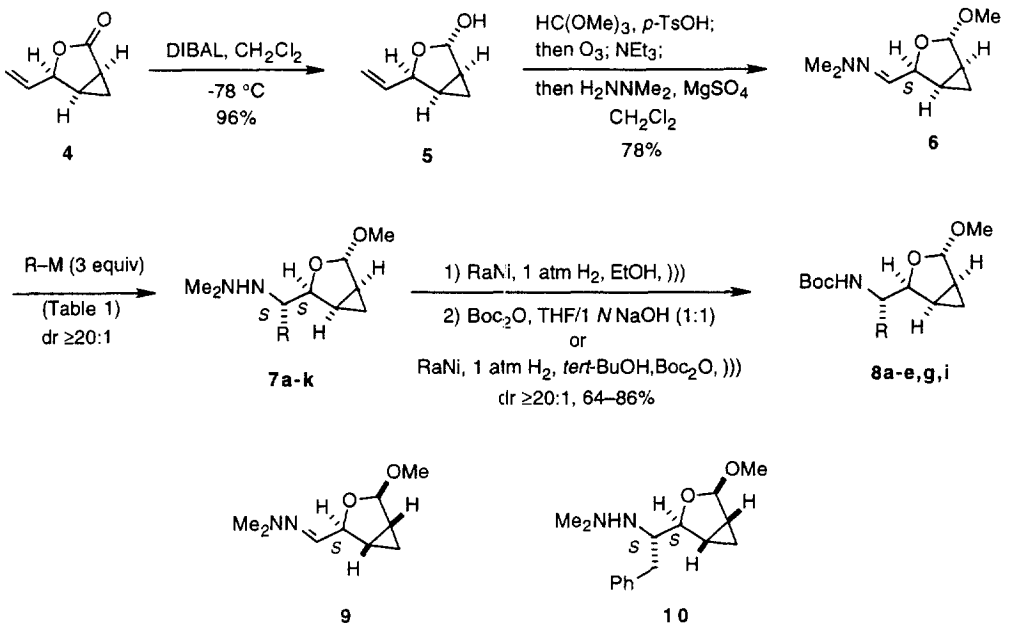
1 **2**: W, X = H, OH **3** **4**

The starting material for these investigations was the enantiomerically pure cyclopropyl lactone **4**, which was prepared in two steps from commercially available divinyl carbinol.[2a] Hydride reduction of **4** gave the lactol **5** (Scheme 2).[3] In a convenient one-pot sequence, the lactol moiety of **5** was protected as a methyl acetal, the vinyl group was converted into a dimethylhydrazone by ozonolysis of the double bond and reaction with dimethylhydrazine to give **6** in 78% overall yield.

The stereoselectivity of the additions of different organometallic reagents to **6** were then examined, and these results are summarized in Table 1. The reactions of alkyllithium reagents in ether or THF and of Grignard reagents in toluene with the hydrazone **6** typically gave the adducts **7** in very good yields and with high levels of diastereoselectivity (dr ≥20:1).[4,5] Primary, secondary, tertiary, vinyl, allyl, aryl and other functionalized organometallic reagents could be used in this transformation. In order to ascertain whether the metal played a role in

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00397-4

Scheme 2



these additions, the reactions of a number organolithium and Grignard reagents with **6** were compared. For example, the additions of R–Li and R–MgX (where R = Bn, *n*-Bu, *i*-Pr, and Ph) to **6** proceeded with comparable efficiencies and selectivities. On the other hand, isobutylmagnesium chloride added to **6** in 81% yield, whereas isobutyllithium added in 36% yield. A more dramatic difference was observed in the additions of methyllithium

Table 1. Additions of Organometallic Reagents R–M to Hydrazone **6**.[6]

compound	R	M	solvent	temp (°C) [time (min)]	yield(%) of **7**
7a	Bn	Li	ether	–10 to rt [120]	71
7b	*n*-Bu	Li	ether	–78 [15]	81
7c	Me	Li	THF	–78 to rt [15]	91
7d	*i*-Bu	MgCl	toluene	rt [40]	81
7e	*i*-Pr	MgCl	toluene	rt [60]	88
7f	*t*-Bu	Li	ether	–78 [5]	83
7g	Ph	Li	THF	–40 to rt [25]	92
7h	CH_2SiMe_2Ph	Li	ether	–78 to rt [20]	47
7i	$(CH_2)_4OTBDMS$[7]	Li	ether	–78 to rt [20]	70
7j	allyl	MgBr	toluene	–40 [60]	83
7k	vinyl	MgBr	toluene	70 [15]	61

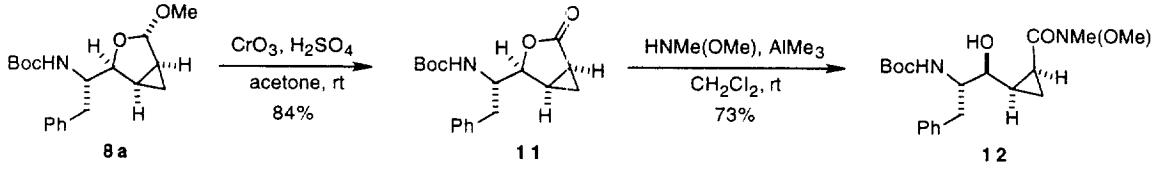
(91%) and methylmagnesium bromide (<5%). Solvent effects were not extensively explored, but we did observe in preliminary experiments that the addition of vinylmagnesium bromide to **6** was more stereoselective in toluene (dr ≥20:1) than in THF (dr = 6:1).

Highly diastereoselective additions of alkyllithium and Grignard reagents to α-heteroatom-substituted hydrazones have been observed previously,[8,9] and the stereochemical course of those reactions was suggested to be chelation-controlled. The observation that the *S*-configuration of the stereogenic center alpha to the hydrazone moiety in **6** induces the *S*-configuration alpha to nitrogen in the adducts **7a-k** is consistent with the preferential nucleophilic attack of the organometallic reagent from the less hindered face of a five- or six-membered chelate. In support of this hypothesis, we found that the addition of benzyllithium to **9** proceeded in the same absolute sense as the corresponding addition to **6** and gave **10** with high diastereoselectivity (73% yield; dr ≥20:1). Thus, the diastereofacial selectivity in organometallic additions to **6** and **9** is determined primarily by the stereochemistry alpha to the hydrazone moiety in **6** and **9**, and the relative stereochemistry at other stereogenic centers on the cyclopentane ring have virtually no effect.

The hydrazines **7a-e,g** were hydrogenolyzed using Raney Nickel as a catalyst, and the intermediate amines were protected as the *tert*-butyl carbamates to give **8a-e,g** in 75–86% yields. Epimerization of the center alpha to the amino group, which presumably arises from oxidation–reduction of the intermediate free amine,[10] may be a problem when hydrazines are reduced with Raney Nickel. Indeed, we observed an erosion in the stereochemistry at this center when **7b** and **7i** were subjected to the usual two-step reduction/protection protocol as illustrated by the obtention of a mixture (4:1) of epimeric amines **8i** from **7i**. A one-pot procedure was thus devised to solve this problem. Thus, when the hydrogenolyses of **7b** and **7i** were conducted in the presence of $(Boc)_2O$, the intermediate amines were protected *in situ*, and the products **8b** and **8i** were isolated without any observable epimerization.

The protected amines **8** are nicely suited for elaboration into peptide mimics of the general type **2**. For example, the acetal moiety in **8a** was hydrolyzed and oxidized with Jones reagent to give the lactone **11**. Elaboration of **11** using a ring opening-amidation procedure we recently developed as a variant of the Weinreb amidation protocol provided the turn mimic **12**.[11]

Scheme 3



In summary, we have demonstrated that dimethylhydrazones related to **6** undergo stereoselective additions with a variety of functionalized organometallic reagents to give adducts that may serve as precursors of pseudopeptides. Applications of this methodology to the synthesis of biologically active pseudopeptides are in progress and will be reported in due course.

Acknowledgments. We thank Pfizer Central Research (Groton, CT) and the National Institutes of Health for generous support of this research.

REFERENCES AND NOTES

1. (a) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710-1721. (b) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Matha, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. *J. Med. Chem.* **1998**, *41*, 1581-1597.
2. a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493-4494. (b) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763-5775. (c) Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521-1524. (d) Martin, S. F.; Hillier, M. C. *Tetrahedron Lett.* **1998**, *39*, 2929-2932.
3. All new compounds were purified (>95%) by distillation, recrystallization, flash chromatography, or preparative HPLC and were characterized by ^{1}H and ^{13}C NMR, IR, and HRMS.
4. The diastereomeric ratios (dr) were determined from ^{1}H NMR analysis of the crude reaction mixtures, and the minor isomer was typically not detected. Given the limitations of the NMR method, the dr is thus > 20:1.
5. **General Procedure for Organometallic Additions to Hydrazone 6**. *Grignard addition*: Hydrazone **6** (0.15–0.20 mmol) was dissolved in freshly distilled (from sodium) toluene (5 mL) and cooled to the indicated temperature, whereupon Grignard reagent (1 3 M, 3 equiv) in Et_2O or THF was added by syringe. *Alkyllithium addition*: The appropriate organolithium reagent (1.6 M, 3 equiv) was diluted with Et_2O or THF (1 mL), and cooled to the indicated temperature. Hydrazone **6** (0.15–0.20 mmol in 1 mL anhydrous Et_2O or THF) was then slowly added by syringe. When starting hydrazone from either organometallic addition was completely consumed (as judged from TLC analysis), saturated aqueous NH_4Cl (5 mL) was added, and the reaction mixture stirred at rt for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude hydrazine was purified by flash chromatography eluting with EtOAc/hexanes or Et_2O/pentane.
6. All reactions were run at 0.15–0.20 mmol scale and the reported yields have been duplicated.
7. For the preparation of the precursor alkyl iodide, see: Heslin, J. C.; Moody, C. J. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1417-1423.
8. (a) Claremon, D. A.; Lumma, P. K.; Philips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265-8266. (b) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277-3284.
9. (a) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563-4565. (b) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038-1050.
10. Nicaise, O.; Denmark, S. *Bull. Soc. Chim. Fr.* **1997**, *134*, 395-398
11. Martin, S. F.; Dwyer, M. P.; Lynch, C. L. *Tetrahedron Lett.* **1998**, *39*, 1517-1520.