1,3-Asymmetric Induction via 1,5-Hydrogen Atom Translocation Reactions. Highly Enantioselective Synthesis of β-Substituted β-Amino Acids

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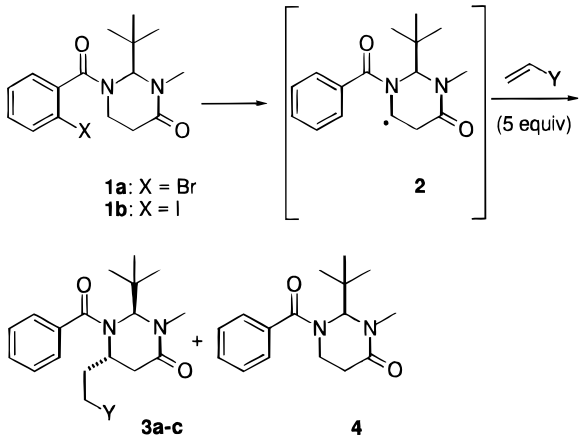
Since the introduction of the 1,5-hydrogen atom translocation as a new mechanistic concept in radical processes,[1] eminent accomplishments by Curran[2a] and De Mesmaeker,[2b] among others,[2c−f] have demonstrated its considerable scope and application for synthetic methodology. As part of our efforts in this active area,[1c,3] we report on the highly (>95:5) diastereoselective transformation of racemic and enantiomerically pure *N*-(*o*-bromo- and -iodobenzoyl)-2-*tert*-butyl-perhydropyrimidinones **1a,b** with electron-deficient alkenes into substituted products **3a**−**c** (Scheme 1). This aryl to α-amidoyl 1,5-radical translocation,[4] tailored for the first time for 1,3-asymmetric induction,[5] offers a new general route for the synthesis of unusually functionalized optically active β-substituted β-amino acids[6a] such as **7, 8** which are of considerable current interest as bioactive natural and unnatural entities and as precursors for β-lactams.[6b]

Racemic *N*-*o*-bromobenzoylperhydropyrimidinone **1a** and the corresponding iodo analogue **1b** were prepared[7] from β-alanine in four steps according to the Juaristi−Seebach protocol for the debromo derivative,[8a] while enantiomerically pure **1a** was obtained from L-asparagine by a route used for the preparation of other enantiopure perhydropyrimidinones.[8b−11] While ^{1}H and ^{13}C NMR spectra of the pyrimidinones **1a,b** displayed high complexity due to restricted rotation about the amide N−CO and Ar−CO bonds,[1c,3] X-ray crystallographic analysis[12] of enantiomerically pure (−)-**1a** (Figure 1) showed the heterocyclic ring in a sofa-like conformation with a quasi axial *tert*-butyl group, similar to that described for the debromo analogue and related derivatives.[13] Thus, in the solid state, the equatorial and axial α-amidoyl hydrogens are located 3.30 and 4.65 Å, respectively, from the bromo atom, and the *tert*-butyl group strongly shields the β-face of the molecule.

Scheme 1



To probe the efficacy of the 1,5-hydrogen atom transfer, pyrimidinone **1a** was subjected to tin deuteride/AIBN conditions to afford deuterated products **5** and **6** (Scheme 2) (89% yield, 53% d_1 by MS) in a 7:3 ratio[14] which is in good agreement with corresponding rotamer populations as determined by variable temperature NMR.[15]

The results of electrophilic olefin-trapping experiments are summarized in Table 1. Using standard tin hydride conditions

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(1) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161. (b) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902. (c) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896−898.

(2) (a) Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1996**, *118*, 3142−3147 and references cited therein. (b) Denenmark, D.; Winkler, T.; Waldner, A.; De Mesmaeker, A. *Tetrahedron Lett.* **1992**, *33*, 3613−3616. (c) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605−615 and references cited therein. See also: (d) Booth, S. E.; Benneche, T.; Undheim, K. *Tetrahedron* **1995**, *51*, 3665−3674. (e) Ikeda, M.; Akamatsu, S.; Kugo, Y.; Sato, T. *Heterocycles* **1996**, *42*, 155−158. (f) Gimisis, T.; Chatgilialoglu, C. *J. Org. Chem.* **1996**, *61*, 1908−1909.

(3) Beaulieu, F. Ph.D. Thesis, University of Waterloo, 1994. Arora, J. M.Sc. Thesis, University of Waterloo, 1995.

(4) For an alternative method of generating α-amidoyl radicals via 1,5-hydrogen atom translocation, see: Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913−5916. Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779−2786. For radical C−C bond formation by photoinduced electron transfer in α-silyl carbamates, see: Meggers, E.; Steckhan, E.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2137−2139. Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219−224.

(5) For 1,2-asymmetric induction via radical intervention, see: Curran, D. P.; Abraham, A. C. *Tetrahedron* **1993**, *49*, 4821−4840.

(6) (a) Review: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (b) Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH: New York, 1993.

(7) β-Alanine was converted into its *N*-methylamide, which was condensed with pivaldehyde to give the Schiff base. Treatment with 2-bromo/iodobenzoic anhydride in Tol at reflux gave heterocycles **1a** and **1b** in 31% and 21% overall yield, respectively.

(8) (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553−2557. (b) For the synthesis of β-alkyl-β-amino acids by metalation/electrophile quench from dihydropyrimidinones, see: Chu, K. S.; Konopelski, J. P. *Tetrahedron* **1993**, *49*, 9183−9190.

(9) (a) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800−1812. (b) Lakner, F. J.; Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *Org. Synth.* **1995**, *73*, 201−214.

(10) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723−726.

(11) Hydrogenation of known (*S*)-2-*tert*-butyl-1-carbobenzyloxy-2,3-dihydro-4(1*H*)-pyrimidinone[9a] at 35 bar hydrogen pressure over Pd−C at room temperature gave the saturated 2-*tert*-butylperhydropyrimidinone in 89% yield. After benzoylation (*o*-bromobenzoyl chloride/NEt_3/THF) followed by *N*-methylation (Me_2SO_4/NaH/THF), (−)-**1a** was obtained in 57% yield after recrystallization. In the preparation of potassium (6*S*)-2-*tert*-butyl-4-pyrimidinone-6-carboxylate from L-asparagine and pivaldehyde, Juaristi and co-workers report a 86:14 *cis:trans* isomeric mixture which is retained upon benzoylation. Acidic workup precipitated the pure *cis* isomer (74% yield) (Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. Submitted for publication in *Tetrahedron: Asymmetry*. We are grateful to Dr. Juaristi for providing us with a copy of this manuscript prior to publication). On the other hand, Konopelski reported the formation only of the *cis* isomer which, upon CbzCl treatment and HCl workup, furnished (2*S*,6*S*)-1-Cbz-6-carboxypyrimidinone.[9a] In the overall conversion of asparagine into this product, we detected (NMR) and isolated only the *cis* isomer.

(12) Crystal data for **(−)-1a**, $C_{16}H_{21}BrN_2O_2$, M_r = 353.26, monoclinic, $P2_1$, a = 8.041(1) Å, b = 7.495(1) Å, c = 14.109(2) Å, β = 99.85(1)°, V = 837.8(3) Å^3, Z = 2, D_c = 1.400 g/cm^3, μ (Mo Kα) = 24.59 cm^{-1}, F(000) = 364, T = 295 K. Data were collected on a Siemens P4 diffractometer with Mo Kα radiation (λ = 0.71073 Å). 3130 reflections were measured giving 2914 independent reflections (1457 Friedel pairs). The structure was solved using Patterson and Fourier routines (SHELXTL Ver.4.2/IRIS) and refined by full-matrix least-squares on F resulting in final R, wR, and GoF (for 2288 data with $F > 4.0\sigma(F)$) of 0.0367, 0.0260, and 1.78, respectively, for solution using the S model (for solution of the R model, final R, and wR values were 0.0675 and 0.0642, respectively).

(13) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913−934.

(14) Determined by integration of the ^{2}H NMR spectra (30.7 MHz).

(15) The ^{1}H NMR spectrum of **1a** in $CDCl_3$ or DMSO-d_6 exhibits four resonances for the *tert*-butyl group at 20 °C (for details, see supporting information). We believe that the split in the major and minor resonances, *e.g.* at 20 °C, is due to restricted rotation about the Ar−C(O) bond, and the major and minor resonances themselves, *e.g.* at 60 °C, are due to the *Z:E* amide isomerization of (O)C−N bond. At 80 °C, the integration of the major and the minor peaks correspond to a ratio of 7:3. Overall coalescence is observed at 100 °C ($\Delta G^{\ddagger}$ = 18.7 kcal/mol).

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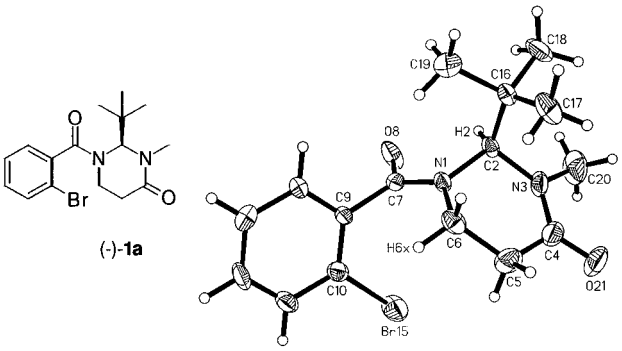


Figure 1.

Scheme 2

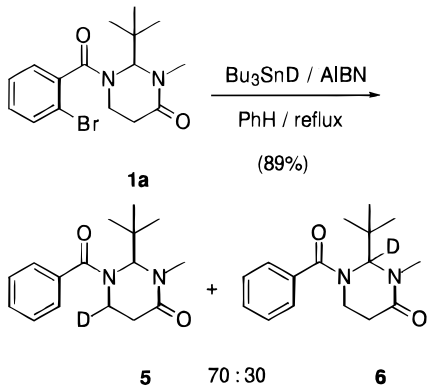


Table 1. α-Amidoyl Functionalization of Racemic Perhydropyrimidinones **1a** and **1b**

X	conditions[a]	addition product (yield, %)[b]	Y	reduction (**4**) (yield, %)[b]
Br	A	**3a** (53)	CO_2Me	41
Br	B	**3a** (62)	CO_2Me	16
I	B	**3a** (63)	CO_2Me	34
Br	B	**3b** (64)	CN	21
I	B	**3b** (42)	CN	57
Br	B	**3c** (40)	SO_2Ph	48
I	B	**3c** (27)	SO_2Ph	70

[a] A: Bu_3SnH (2 equiv)/AIBN (cat)/alkene (5 equiv)/PhH/reflux (standard conditions). B: Bu_3SnCl (0.1 equiv)/$NaCNBH_3$ (2 equiv)/AIBN (cat)/alkene (5 equiv)/*t*-BuOH/reflux. [b] All yields refer to isolated and purified (chromatographed) materials. In all cases, ^{1}H NMR spectra of crude materials showed the presence of only one isomer (dr > 95:5).

in the presence of methyl acrylate,[1c] the bromoperhydropyrimidinone **1a** cleanly furnished a mixture of addition product **3a** (53% yield, >90% diastereoselectivity) and reduced material **4** (41%). By the application of the catalytic tin method,[16] the yield of the addition product **3a** (62%) was improved and the amount of reduction product **4** (16%) was considerably decreased. In the presence of acrylonitrile and phenyl vinyl sulfone as acceptor olefins, the radical interception products **3b** and **3c** were obtained from **1a** in 64% and 40% yields, respectively, together with 21% and 48% reduced material **4**. Trapping the α-amidoyl radical derived from the iodo compound **1b** with these alkenes led to predominant amounts of **4**. The substantial difference in amounts of reduction product between the iodo and the bromo derivatives is not understood and needs further investigation.

When optically active (−)-**1a** was subjected to the catalytic tin hydride conditions, the substituted products **3a**−**c** were obtained in acceptable yields (similar to the racemic series) and high enantiomeric purity (Table 2).[17]

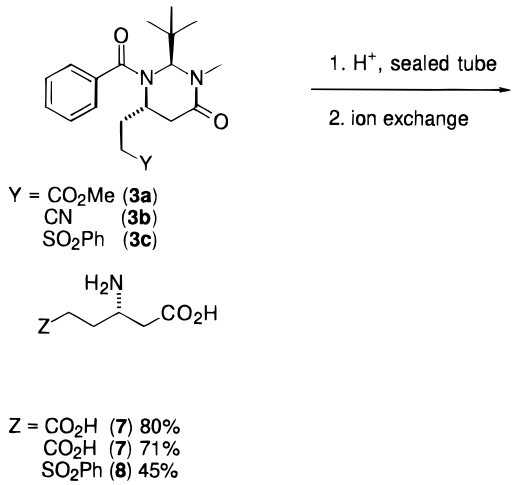
(16) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

Table 2. 1,5-Hydrogen Atom Transfer in Optically Active *N*-(*o*-Bromobenzoyl)-*tert*-butylpyrimidinone **(−)-1a** using the Catalytically Tin Hydride Method[a]

addition product	Y	yield, %[b]	ee, %	reduction (**4**), %[b]
3a	CO_2Me	56	97	10
3b	CN	59	97	20
3c	SO_2Ph	50	98	41

[a] Bu_3SnCl (0.1 equiv)/$NaCNBH_3$ (2 equiv)/AIBN (cat)/alkene (5 equiv)/*t*-BuOH/reflux. [b] All yields refer to isolated and purified (chromatographed) materials. By ^{1}H NMR spectroscopy all crude products showed the presence of only one isomer (dr >95:5); ee's were measured on the single pure isomers **3a**−**c**, obtained by flash chromatography.

Scheme 3



To demonstrate the utility of the 1,5-hydrogen atom translocation for the synthesis of optically active β-amino acids, compounds **3a**−**c** were treated under acid-catalyzed conditions[8a] followed by purification by acidic ion-exchange resin to afford 3-aminoadipic acid **7**[18] and the δ-sulfonyl-substituted analogue **8** in 45−80% yields (Scheme 3).[19]

In summary, a new highly diastereoselective transformation, **1** → **3,** mediated by 1,5-hydrogen atom translocation (**2**), has been uncovered. Its generality and application to the synthesis of β-substituted β-amino acids **7**, **8** has been demonstrated. The broader conceptualization of this 1,3-asymmetric induction radical process and its application in the design and construction of optically active, biologically important natural and unnatural β-amino acids and β-lactams may be anticipated.

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Supporting Information Available: Detailed description of experimental procedures for the preparation and reactions of **1**, **3a**−**c**, **4**, **7**, **8**; ^{1}H-NMR spectra of **1a**, **3a**−**c**, **7**, **8**, and X-ray data of **1a** (26 pages). See any current masthead page for ordering and internet access instructions.

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(17) An (*S*,*S*)-Whelk-O1 chiral column was used. Enantiomeric purity assays were completed with both racemic and enantioenriched materials and repeated at least once in order to ensure accuracy of the method used. For details, see supporting information.

(18) Obtained from Sigma/Aldrich as the racemate.

(19) For the synthesis and biological properties of amino sulfonic acids, see *e.g.*: Braghiroli, D.; Mussati, E.; Di Bella, M.; Saladini, M. *Tetrahedron: Asymmetry* **1996**, *7*, 831−836 and references cited therein.