Preparation of Nonracemic 3,5-Disubstituted-γ-butyrolactones: An Effective Sequent Auxiliary for Amide Alkylation and Iodolactonization

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Summary: The effective dual use of a chiral auxiliary in two sequential steps is reported; this sequent auxiliary mediates diastereoselective C–C bond formation in the first step and mediates diastereoselective heterocyclization in the second step.

Development of a synthetic strategy wherein a single chiral auxiliary moiety is called upon to mediate more than one diastereoselective transformation would lead to significantly improved synthetic economy and atom efficiency. Orchestrating such an event in a context where the chiral auxiliary delivers an optically pure target molecule with both diverse functionality and controlled relative stereochemistry would further enhance the strategic advantage. We envisioned the enantioselective two-step conversion of substrate **I** to γ-butyrolactone **III** as an ideal candidate for evaluating the synthetic potential of this *sequent auxiliary* concept (Figure 1; AUX mediating diastereoselective C–C bond formation in step 1 and diastereoselective heterocyclization in step 2 to yield optically pure substrate **III**).

The use of nitrogen-based auxiliaries to control step 1 is well documented,[2,3] and insight into managing the selectivity of step 2[4] came with Yoshida's discovery that an *N,N*-dialkylamide[5] auxiliary greatly improved the diastereoselectivity of **II** → **III** (AUX = –OH vs $-NMe_2$ being ≈ 1:2 vs 9:1, respectively). Building on these leads, we sought an auxiliary moiety which would mediate both step 1 and step 2, ideally effecting each transformation with complete stereocontrol, and report herein the realization of that goal.

N,N-Disubstituted amides are known to undergo enolization with complete Z-enolate selectivity[2b] and consequently simplify diastereoselective Cα-alkylation to a question of *re-* versus *si*-face selectivity. With this in mind, only nitrogen heterocycles were selected as sequent auxiliaries to mediate **I** → **II** → **III** (auxiliaries depicted in Table 1). In all cases, enolate formation (LDA, THF, –78 °C) followed by addition of the electrophile (–78 °C → rt) delivered the Cα-alkylated amide in excellent chemical yield (80–90%). Product evaluation (^{1}H-NMR of amides **1**–**8** and subsequent GC analysis of the resulting iodolactones **9** and **10**; see Table 2) revealed that the commercially available L-prolinol auxiliary[6] gave the poorest diastereoselectivity (**I** → **1/2**) and that the C_2-symmetric piperidine[3a] (**I** → **3/4**) and oxazolidinone[7] (**I** → **5/6**) auxiliaries gave generally high selectivity but yet exhibited some electrophile-based variability. In contrast, employing (2*R*,5*R*)-bis[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]pyrrolidine, a C_2-symmetric pyrrolidine auxiliary prepared from D-mannitol by modification

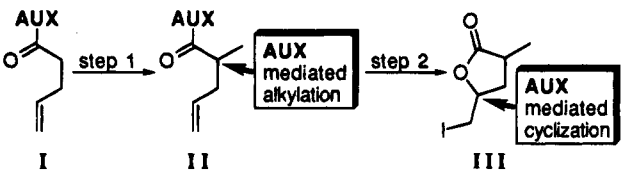
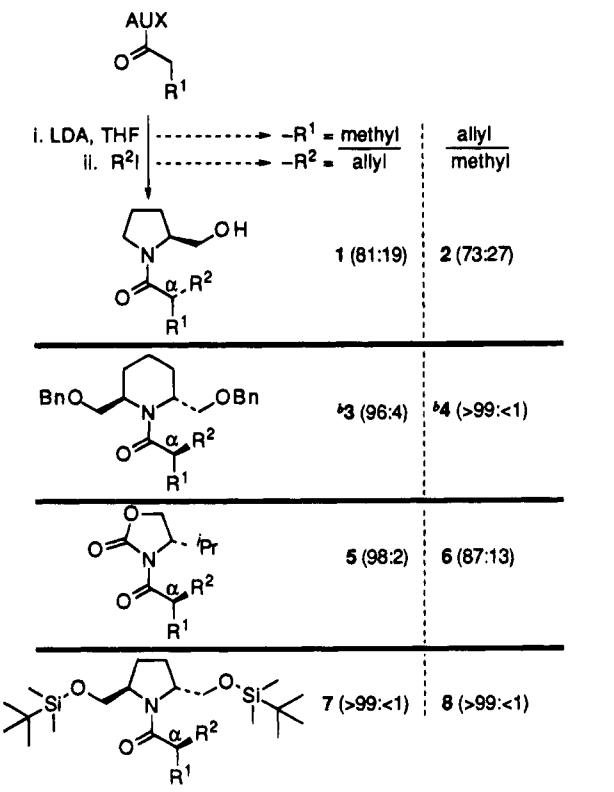


Figure 1.

Table 1. Auxiliary-Mediated Alkylation of Amides[a]



[a] In each case, the major diastereomer is depicted and the minor diastereomer is epimeric at Cα. [b] The C_2-symmetric piperidine auxiliary used here had an optical purity of 76%.

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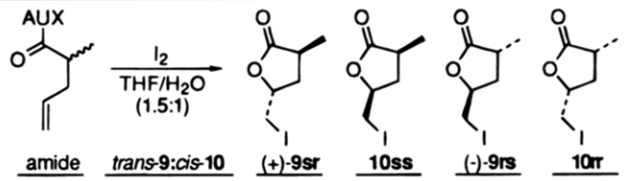
Table 2. Auxiliary Mediated Kinetic Iodolactonizations[a]



amide	*trans*-9:*cis*-10	(+)-9sr	10ss	(-)-9rs	10rr
1	92:8	68	5	24	3
2	92:8	17	2	75	6
[b] 3	90:10	11	2	79	8
[b] 4	94:6	83	5	11	1
5	78:22	2	0	76	22
6	88:12	77	10	11	2
7	>99:<1	0	0	100	0
8	>99:<1	100	0	0	0

[a] Product ratios determined by capillary GC analysis using a β-cyclodextrin on OV-1701 column (30 m × 0.25 μm, isothermal at 95 °C): t_R **9rs** = 92.0 min, t_R **9sr** = 94.3 min, t_R **10ss** = 92.4 min, t_R **10rr** = 93.7 min. [b] The C_2-symmetric piperidine auxiliary used here had an optical purity of 76% **ee**.

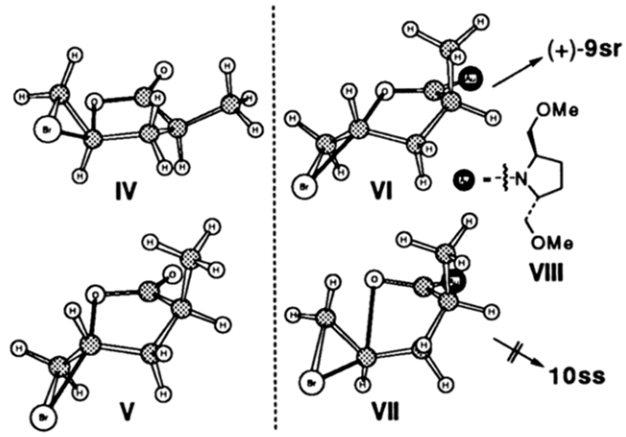


Figure 2. Electrophilic cyclization transition states. See refs 11 and 12. For clarity, auxiliary **VIII** has been removed from these presentations of **VI** and **VII**.

of chemistry developed by Marzi,[8] resulted in completely stereoselective Cα-alkylation (**I** → **7/8**) regardless of whether the electrophile was iodomethane or 3-iodopropene.

The pentenamides obtained from step 1 (**1**−**8**) were subjected to kinetic iodolactonization conditions [3 equiv of iodine, THF/H_2O (1.5:1), rt] to evaluate the efficacy of each auxiliary in controlling step 2. Positioning the Cα-methyl substituent in a pseudoaxial orientation (See Figure 2) is paramount to the stereoselective mediation of step 2,[5a] and it was this requirement we hoped to fulfill with the four auxiliaries shown in Table 1. Moreover, we hoped that interplay between the Cα-stereocenter and the stereogenic auxiliary (*cf.* **1** versus **2**) would not lead to matched and mismatched selectivities.

In that regard, we were pleased to find that L-prolinol-derived amides **1** and **2** were both *trans*-selective. However, the degree of selectivity (92:8::*trans*:*cis*) was disappointing. The differences in selectivity between piperidine-derived amides **3** versus **4** (90:10 versus 94:6::*trans*:*cis* selectivity, respectively) and oxazolidinone amides **5** versus **6** (78:22 versus 88:12::*trans*:*cis* selectivity, respectively) suggested the increasing interference of double diastereoselectivity. We were therefore gratified to find that pyrrolidine-derived amides **7** and **8** undergo 100% stereoselective *trans*-iodolactonization in 87−90% yield. *Taken in concert, the 100% stereoselective Cα-alkylation of step 1 with the 100% stereoselective cyclization of step 2, this pyrrolidine-based sequent auxiliary delivers either antipode of* **9** *with complete optical purity!*

In contrast to amides **1**−**8**, kinetic iodolactonization[9] of 2-methyl-4-pentenoic acid proceeds with poor selectivity favoring the *cis*-isomer (**9**:**10**::1:2.1).[10] AM1 quantum mechanical calculations[11] suggest that transition states[12] **IV** and **V** (Figure 2) represent the competing pathways for the electrophilic cyclization (bromolactonization)[11b] of this acid and account for the poor selectivity (**IV** favored by 0.307 kcal/mol). Calculation of transition states[12] incorporating pyrrolidine-based auxiliary **VIII** in the cyclization of amides show that conformational biases caused by the interplay between this auxiliary and the Cα-stereogenic center force the Cα-methyl substituent to adapt a pseudoaxial orientation in both competing transition states. In so doing, the auxiliary has the effect of refocusing the transition state competition from methyl-*equatorial* **IV** versus methyl-*axial* **V** ($\Delta H_{f[IV-V]} = -0.307$ kcal/mol) to methyl-*axial* **VI** versus methyl-*axial* **VII** ($\Delta H_{f[VI-VII]} = -2.30$ kcal/mol). The exceptional selectivity obtained with our sequent auxiliary in amides **7** and **8** corroborates this analysis.

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Supplementary Material Available: Experimental details for the preparation of **7** and **8**, experimental details for the iodolactonizations of **1**−**8**, ^{1}H- and ^{13}C-NMR spectra for (*R*,*R*)-2,5-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidine, and ^{1}H-NMR spectra for **7** and **8** (11 pages). This information is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) (a) Transition state geometries were optimized using the AM1 Hamiltonian on Spartan software: Spartan version 3.0.1, copyright 1991/1992/1993, Wavefunction Inc., 1804 Von Karman, Suit 370, Irvine, CA 92715 [(714)955−2120]. Initial guesses at the transition state geometries were designed using the Builder program in Insight II, version 2.3.0, Dec 1993, from Biosym Technologies of San Diego. (b) The AM1 Hamiltonian in Spartan 3.0.1 is not parameterized for iodine.

(12) Frequency analysis confirms one negative eigenvalue for each of these optimized geometries.