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Raney-Co Mediated Reductive Cyclization of an α,β-Unsaturated Nitrile

Jacob M. Janey,* Charles J. Orella, Eugenia Njolito, Jenny M. Baxter, Jonathan D. Rosen, Michael Palucki, Rick R. Sidler, Wenjie Li, Jason J. Kowal, and Ian W. Davies

Department of Process Research, Merck Research Laboratories, Merck and Co., Inc., Rahway, New Jersey 07065

jacob_janey@merck.com

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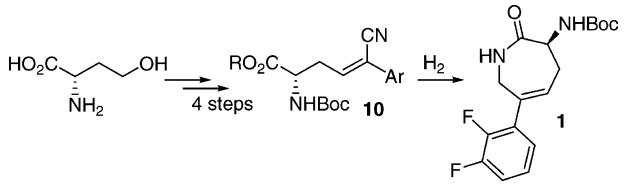
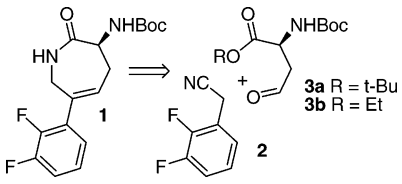


An expedient, five step synthesis of caprolactam **1** is reported starting from natural L-homoserine. The key step is a chemoselective reductive cyclization of α,β-unsaturated nitrile **10** mediated by Raney-Co type metals. This hydrogenation is extensively investigated in order to account for the observed product distribution and yields.

Introduction

The reduction of α,β-unsaturated nitriles to allylic amines is a very important and yet underutilized organic transformation. The importance of the reaction can be traced directly to the value of the allylic amine moiety as a synthetic intermediate[1] or in a final product.[2] The ability to easily prepare α,β-unsaturated nitriles via a condensation reaction between readily available carbonyls and α nitrile centers provided the impetus to develop an efficient and selective reduction of α,β-unsaturated nitriles to allylic amines. The development of such a process poses several significant challenges. The first challenge is the need to address chemoselectivity.[3] The relatively electron deficient olefin is quite prone to reduction under a variety of conditions including the traditional metal hydride methods for reduction of saturated nitriles to amines.[4] A second challenge to developing the desired transformation is the undesired formation of secondary and tertiary amine dimeric and trimeric side products.

SCHEME 1. Retrosynthesis of Caprolactam 1



Our interest in this problem was initiated by the desire to develop an efficient synthesis of unsaturated caprolactam **1**, an advanced intermediate in the synthesis of a Merck drug candidate (Scheme 1). We believed that efficient access to this caprolactam could be achieved via an aldol condensation between commercially available nitrile **2** and an amino acid derived aldehyde **3**, followed by a nitrile reduction (and perhaps cyclization) of the resulting α,β-unsaturated nitrile. Therefore, the identification of an efficient, chemoselective nitrile reduction was the crucial step toward realizing a successful synthesis.

(1) For example, see the isomerization of allylic amines in the Takasago process: (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600−601. (b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208−5217. (c) Takabe, K.; Uchiyama, Y.; Okisaka, K.; Yamada, T.; Katagiri, T.; Okazaki, T.; Oketa, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5253−5254.

(2) For a general review on primary allylic amine synthesis, see Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685−700.

(3) Kukula, P.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.* **2004**, *346*, 1487−1493.

(4) For a thorough review of nitrile reduction conditions, see *Comprehensive Organic Synthesis*, Vol. 8; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; pp 251−254.

(5) (a) Ozinskas, A. J.; Rosenthal, G. A. *J. Org. Chem.* **1986**, *51*, 5047−5050. (b) Baldwin, J. E.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3605−3608. (c) Keith, D. D.; Tortora, J. A.; Ineichen, K.; Leimgruber, W. *Tetrahedron* **1975**, *31*, 2633−2636.

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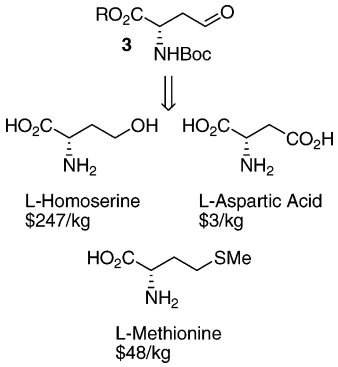
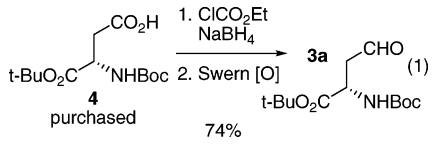
SCHEME 2. Precursors Available from the Chiral Pool



Results and Discussion

The first priority was the development of an efficient, scalable synthesis of amino acid aldehyde **3** (Scheme 2). We felt that the most efficient means of accessing this aldehyde would be from suitable amino acids available from the chiral pool given the naturally derived stereochemistry. The most convenient starting material is L-homoserine, which is readily available (comercially or from L-methionine) and can be easily protected and oxidized to the desired aldehyde.[5] From a cost perspective, L-aspartic acid would be the ideal starting amino acid, but it would require the development of a regioselective esterification followed by an acid reduction to the aldehyde.

Aspartic acid is clearly the most inexpensive relevant starting amino acid, thus we examined the conversion of this amino acid to the desired aldehyde. Treating commercially available *N*-Boc aspartic acid *tert*-butyl ester **4** with ethyl chloroformate followed by $NaBH_4$ gave the crude homoserine which could then be oxidized under Swern conditions to the expected aldehyde **3a** in 74% yield over two steps (eq 1).[6] Although this

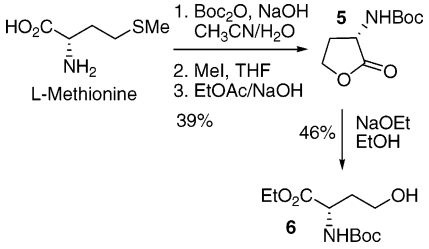


route provided material for early investigations, the *tert*-butyl ester moiety of this aldehyde (**3a**) proved necessary for this reduction−oxidation but an unsuitable choice of ester for the subsequent chemistry. In addition, the commercial availability and cost associated with **4** proved to preclude its use.

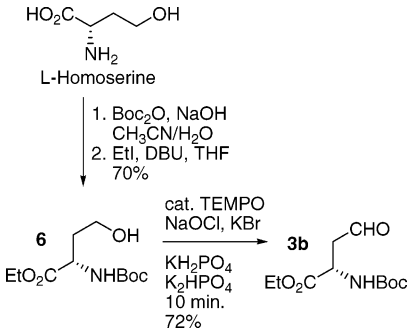
We had also hoped to utilize L-methionine as a starting material as this has been perviously utilized in the synthesis of L-homoserine.[5a,b] Indeed L-methionine can be protected with Boc_2O and then lactonized by activation with iodomethane to give *N*-Boc lactone **5** in low yield (Scheme 3). Unfortunately, lactone **5** is quite resistant to opening with NaOEt and gives the desired homoserine ethyl ester **6** in only moderate yields.

We were able to develop an efficient large scale synthesis of the desired aldehyde **3b** begining with 4 kg of L-homoserine (Scheme 4). The amino acid was protected with Boc_2O followed by esterification with iodoethane in 70% overall yield to give protected homoserine ethyl ester **6**. The usual means of oxidizing homoserine esters, such as **6**, involve either PCC or Swern conditions as those oxidations limit the amount of lactonization

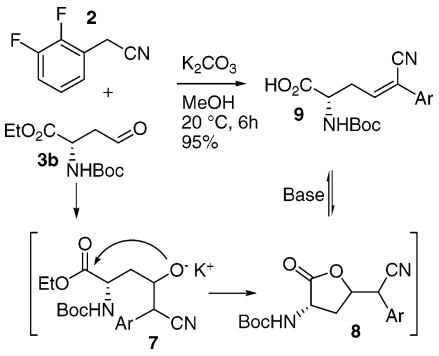
SCHEME 3. Synthesis of Homoserine from Methionine



SCHEME 4. Conversion of Homoserine to Aldehyde 3b



SCHEME 5. Nitrile Aldol Condensation with K_2CO_3 in Methanol



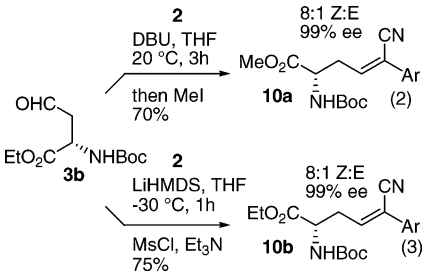
to **5** that is typically seen with other types of oxidents. To avoid the use of super stoichiometric amounts of chromium derived reagents or cryogenic Swern conditions, we carefully developed a TEMPO-catalyzed bleach oxidation protocol. The key to this procedure is the careful control of pH with phosphate buffers as very basic pH provides lactonization and acidic pH provides overoxidation to aspartic acid along with decomposition of the bleach. In this manner, we were able to isolate the desired aldehyde **3b** in 72% yield with acceptable levels of purity on a large scale.

With significant quantities of aldehyde **3b** available from homoserine, the aldol condensation between nitrile **2** and aldehyde **3b** was examined. The condensation under standard conditions with K_2CO_3 in MeOH proceeds cleanly to give, unexpectedly, the free acid **9** in 95% yield. After workup and isolation, upon standing, this free acid was found to undergo a conjugate addition to lactone **8**. This lactonization is reversible, since subjecting lactone **8** to the reaction conditions regenerates the free acid **9**. It is clear that the initially formed potassium alkoxide **7** undergoes immediate lactonization onto the ethyl ester to generate lactone **8**. Lactone **8** then forms the free acid **9** via an E2 elimination (see Scheme 5).

Our initial strategy to address this problem was to develop a simple one-pot procedure for condensation and re-esterification. Indeed, we found that conducting the aldol condensation in THF

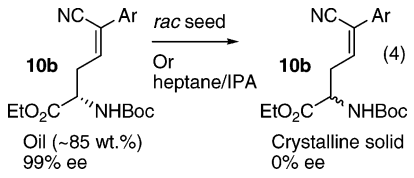
(6) (a) Salituro, G. M.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 760−770. (b) Ramsamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42−43. (c) Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243−8246.

with DBU as a base followed by addition of iodomethane gives the expected methyl ester unsaturated nitrile **10a** in 70% yield with 8:1 Z:E selectivity and no loss of enantiopurity (eq 2).



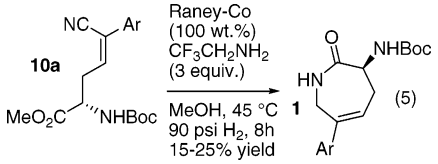
This procedure, though simple, does generate some of the ethyl ester **10b** as well due to incomplete lactonization/elimination. Upon further development work, an improved protocol was developed which involves first deprotonation of the aryl acetonitrile **2** with LiHMDS in THF followed by addition of the aldehyde **3b** to give an intermediate lithium alkoxide which is less prone to lactonization at lower temperatures (eq 3). This lithium alkoxide is then trapped by addition of MsCl and eliminated with triethylamine in an efficient one-pot procedure. In this manner, ethyl ester **10b** was isolated in 75% assay yield with 8:1 Z:E selectivity.

The crude ethyl ester **10b** is an oil at 85 wt % (Z-isomer), and therefore attempts at purification through crystallization were made. Unfortunately, crystallization from heptane/*i*-PrOH or treatment of the crude oil with a seed of crystalline racemate caused a complete turnover of this oil to a racemic, crystalline solid in a dynamic process, despite the neutral conditions (eq 4).



Thereafter, preparative chromatography was used to obtain pure material required for the nitrile reduction.

We believed that the chemoselective reduction of nitrile **10**, though difficult, was possible given the recent examples reported by Blaser and co-workers.[3] They had shown that cinnamonitrile can be efficiently reduced to the desired allylic amine using catalytic Raney-Co catalyst doped with a mix of Cr, Fe, and Ni in the presense of ammonia in methanol. Their best conditions realized a 90% conversion with 80% selectivity for the allylic amine.[7] Initial screening of a few Raney metal catalysts for the reduction of methyl ester unsaturated nitrile **10a** revealed that Raney-Co was chemoselectively reducing the nitrile, but rather than giving the expected allylic amine, the desired unsaturated caprolactam **1** was being formed during the reaction (eq 5).

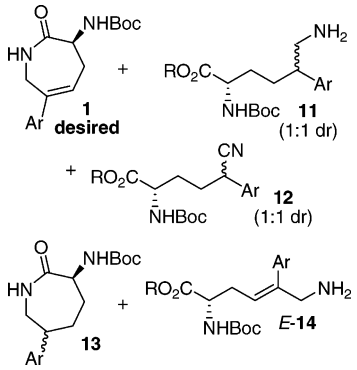


While not without precedent,[8] this reductive cyclization provided a promising lead with which to initiate a high-throughput effort in order to optimize this transformation.

TABLE 1. Summary of Reaction Variables Screened

heterogeneous catalysts	solvents	additives
Rh	H_2O	MCO_3
Ru	**MeOH**	alumina
Fe	THF	**Et_3N**
Pt	*i*-PrAc	AcOH
V	toluene	***i*-Pr_2NH**
Pd	EtOH	**Et_2NH**
Ir	**THF/H_2O**	dabco
Raney-Ni		DMAP
RaCo 2700		pyridine
RaCo 2724		morpholines
		imidazoles

SCHEME 6. Reaction Products Observed after Nitrile Reduction



This nitrile substrate (**10**) contains several functionalities which provide a challenge beyond the issue of chemoselectivity (exacerbated by the electron withdrawing aryl group). While the ester moiety is helpful in that the allylic amine, once generated, can cyclize rather than dimerize (or trimerize), it is also prone to saponification and amidation. This obviates the use of ammonia or hydroxide bases as used by Blaser.[3] It also necessitates dry conditions, as water can lead to the free acid which can then complex quite strongly to cobalt. We were also concerned that alcoholic solvents in the presence of base can lead to slow racemization of the starting nitrile **10** throughout the reaction course. Furthermore, we were not certain as to what effect the E:Z ratio would have on the reaction.

With these issues in mind, we proceeded to screen a library of 24 heterogeneous catalysts on a variety of supports in combination with a variety of solvents and bases with a rapid mass spectrometer assay to quickly probe which conditions gave caprolactam **1** as a major product (Table 1). We quickly narrowed the reaction conditions as Raney-Co type catalysts clearly gave the best results with Fe, Cr, Ni doped Raney-Co 2724 giving the best results. Many metals, in particular Raney-Ni catalysts of all types, gave overreduction to the saturated primary amine **11**, whereas Rh and Pd catalysts gave exclusively olefin reduction to the saturated nitrile **12** (Scheme 6). We also attempted $NaBH_4/CoCl_2$[9] reductions in addition to other metal hydrides, including Buchwald's asymmetric Cu(I)/PMHS conditions[10] and found solely olefin reduction to **12** with no

(7) For another example highlighting the chemoselectivity of Raney-Co versus Raney-Ni, see Fukatsu, K.; Uchikawa, O.; Kawada, M.; Yamano, T.; Yamashita, M.; Kato, K.; Hirai, K.; Hinuma, S.; Miyamoto, M.; Ohkawa, S. *J. Med. Chem.* **2002**, *45*, 4212−4221.

(8) Culbertson, T. P.; Sanchez, J. P.; Gambino, L.; Sesnie, J. A. *J. Med. Chem.* **1990**, *33*, 2270−2275.

(9) (a) Osby, J. O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67−72. (b) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555−4558.

TABLE 2. Temperature Effects on Reduction of Nitrile 10a[a]

wt % catalyst	temp (°C)	pressure (psi)	time (h)	yield **1** (%)	**11** (%)	**14** (%)	**13** (%)	conversion of **10** (%)	mass balance (%)	**1** select (%)
80	110	100	1	7	20	0	11	95	45	18
40	110	100	1	3	16	0	10	80	52	12
80	90	100	2	10	19	0	8	99	37	29
40	90	100	2	6	19	0	12	89	50	17
80	70	100	6	15	23	0	9	99	47	33
40	70	100	6	9	23	0	14	96	49	21
100	40	350	6	9	8	0	5	55	71	43
100[b]	25	400	6	7	7	3	5	44	83	33

[a] 100 mg/mL **10a** in MeOH with 1.5 equiv of Et_3N. [b] Prereduced Raney-Co 2724.

TABLE 3. Temperature Effects on Reduction of Nitrile 10a at 50 mg/mL[a]

wt % catalyst	temp (°C)	pressure (psi)	time (h)	yield **1** (%)	**11** (%)	**14** (%)	**13** (%)	conversion of **10** (%)	mass balance (%)	**1** select (%)
150	40	450	8	44	22	3	7	97	76	60
150	25	450	8	18	12	4	5	81	60	48
100	−20	1000	18	3	4	3	1	67	54	30

[a] No prereduction of Raney-Co 2724, 50 mg/mL **10a** in MeOH, and 1.5 equiv of Et_3N.

enrichment at the newly formed nitrile stereocenter. Thereafter, we focused our research efforts on optimization of Raney-Co mediated reduction conditions.

The hydrogenation was then examined to determine the effects of temperature, substrate concentration, and catalyst loading with or without prereduction of the Raney-Co. The initial screening results indicated that 6−8 h was required to achieve high conversion, with 1−1.5 equiv of base (Et_3N, Et_2-NH, or *i*-Pr_2NH) and doped Raney-Co 2724. Triethylamine was found to be the base of choice, as it gave less racemization of the stereocenter although lower reactivity compared to secondary amine bases.

The effect of reaction temperature was significant, and it was quickly recognized that the both the yield and the chemoselectivity for the nitrile reduction was temperature dependent (Table 2). Lower temperature improved the selectivity, although the reaction rate was depressed as well. At higher temperatures, conversion of starting nitrile **10** was complete, yet the material balance was quite poor. This is probably a reflection of the formation of some secondary and higher amines along with many other oligiomeric products as confirmed by careful LC−MS analysis. Reducing the temperature significantly reduced the amount of saturated caprolactam **13**, while also reducing the amount of saturated amine **11**. The selectivity for nitrile reduction improved at lower temperature, although the selectivity for the desired unsaturated caprolactam **1** was still below 50% in all cases. Even at conversion of only 50%, significant levels of saturated amine **11** and caprolactam **13** were observed. This contrasts with the published results of Blaser et al. for cinnamonitrile, where olefin reduction was observed to take place after most of the nitrile had been reduced to the allylic amine.

In order to reduce the amount of oligiomeric byproducts, the effect of a lower concentration was investigated (Table 3). A concentration of ∼50 mg/mL gave improved yield at elevated temperatures and also improved the selectivity between nitrile reduction and olefin reduction. Lower temperatures did not lead to higher yield or selectivity.

A profile of a reaction carried out at over 40−70 °C indicated that isomerization around the olefin **10a** was evident at times as early as 5−10 min into the reaction (see Table 4). The consequence of this olefin isomerization is that the *E*-nitrile **10** is reduced to an *E*-allylic amine **14** which is incapable of cyclization and thereby reduces the overall yield of unsaturated caprolactam **1**, which only is formed by reduction of the *Z*-nitrile **10**.

TABLE 4. Reaction Profile over Time[a]

temp (°C)	time (h)	yield **1** (%)	**11** (%)	**14** (%)	**13** (%)	conversion of **10** (%)	mass balance (%)	**1** select (%)
36	0.1	3	0	9	0	34	103	24
70	0.5	5	0	20	4	79	67	17
70	1.5	9	0	30	7	98	72	21
70	2	10	0	31	4	100	67	24
70	3	11	0	31	6	100	75	24

[a] 30 mg/mL **10a** in MeOH, 1.5 equiv of Et_3N, 150 wt % Raney-Co 2724 (prereduced), and 100 psi H_2.

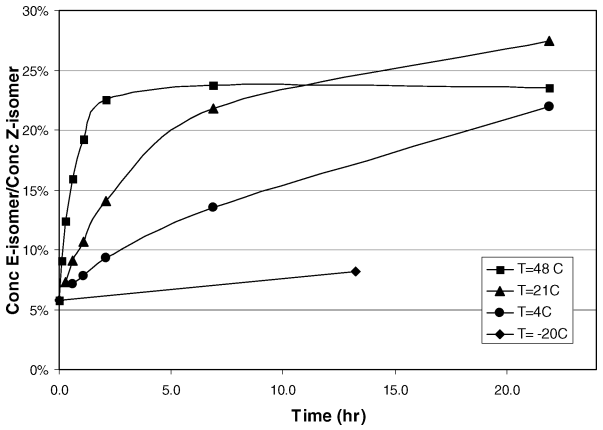


FIGURE 1. Isomerization of *Z*-**10a** to *E*-**10a** with triethylamine from −20 to 48 °C.

For this unsaturated nitrile, the isomerization of *Z*-nitrile **10** to *E*-nitrile **10** is clearly taking place at a rate competitive with reduction (Figure 1). Further, concentrations of caprolactam **1**, *E*-amine **14**, and saturated caprolactam **13** appear to plateau at relatively constant levels, suggesting that reduction of the olefin in the caprolactam **1** and *E*-amine **14** was not significant. The early appearance of saturated caprolactam **13** along with the

(10) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821−5823 and references cited therein.

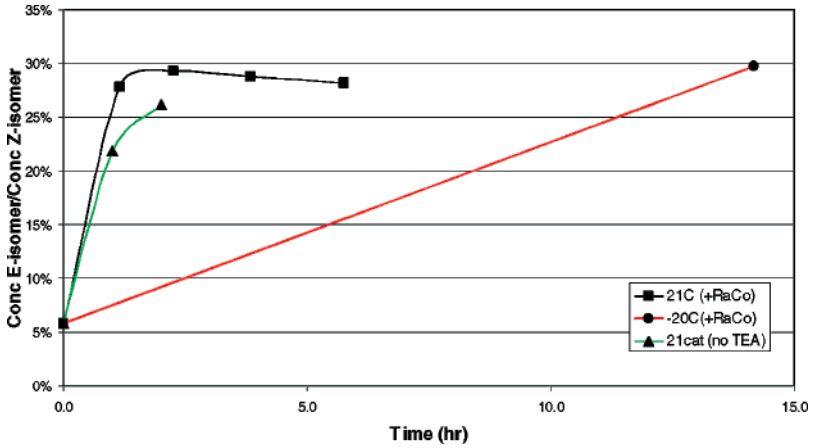
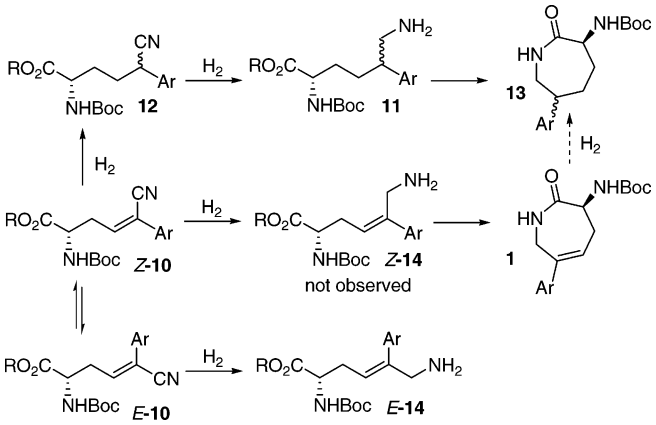


FIGURE 2. Isomerization of *Z*-**10a** to *E*-**10a** with triethylamine and Raney-Co.

SCHEME 7. Possible Origins of Observed Side Products during Reduction



stability of the *E*-amine **14** to these reduction conditions suggests that there is competitive reduction of the olefin moiety in parallel with reduction of the nitrile, followed by reductive cyclization of the saturated nitrile **12** to give the saturated caprolactam **13**.

Further, in the presence of Raney-Co, with or without base, the isomerization of **10a** was enhanced (Figure 2). Even at room temperature, 20% of the *Z*-isomer **10a** was isomerized to *E*-isomer **10a** within 1 h.

The mechanistic picture that emerges from this data and observation is depicted in Scheme 7. The main competing pathways away from the desired caprolactam are olefin reduction caused by incomplete chemoselectivity with Raney-Co 2724 and isomerization from *Z*-**10** to *E*-**10** nitrile which gives rise to the observed side products (excluding oligiomerization).

Thus, we observed that isomerization was the most significant side-reaction that even under the best conditions led to a minimum of 30% conversion of the *Z*-nitrile **10** to the *E*-nitrile **10**. Unfortunately, all attempts to isomerize and subsequently cyclize the *E*-amine isomer **14** to the caprolactam were unsuccessful. As a result of this *Z*- to *E*-olefin isomerization of the starting nitrile, the optimized yield of the nitrile reduction step was 50%. Attempts at limiting isomerization by switching to nonprotic solvents or milder bases at low temperature were largely unsuccessful as no nitrile reduction was observed, indicating the vital role that methanol solvent and amine plays in this reduction.

Conclusion

In summary, the reduction of a α,β-unsaturated nitrile to an allylic amine followed by subsequent lactamization to an advanced unsaturated caprolactam intermediate has been achieved, albeit in moderate yields. Although we successfully realized an expedient, efficient synthesis of the unsaturated nitrile **10**, the Raney-Co reduction of this particular nitrile was quite challenging since rapid olefin isomerization during the hydrogenation along with double bond reduction pathways and oligiomerization were competing with the desired nitrile reduction and cyclization. Many of these side reactions can be attributed to the rather basic conditions in methanol that is required to allow this hydrogenation to proceed. A more chemoselective metal catalyst which allows for the reduction to occur in a less basic reaction media would be required to make this a more efficient, viable process. Despite these difficult circumstances, we were able to develop, through careful screening and optimization, a nitrile reduction which gave 100% conversion of the starting material and 50% yield of the desired unsaturated caprolactam **1** while still retaining the stereointegrity of the amino acid derived center.

Experimental Section

***N*-Boc L-Homoserine.** A 100 L round-bottomed flask was charged with acetonitrile (34 L) followed by addition of solid L-homoserine (4.00 kg, 33.6 mol). To this mixture was added 1 N NaOH (33.6 L). The resulting solution was then cooled to <5 °C with an ice/water bath. A solution of Boc_2O (7.69 kg, 8.10 L, 35.5 mol) in CH_3CN (8.1 L) was then added over a 1 h period via an addition funnel. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2−3 days. The reaction mixture was then concentrated in vacuo (26−28 Torr at 30−35 °C) to a volume of 34 L. This mixture was then cooled to 5 °C with an ice/water bath, and 2.5 N HCl was added over 1 h until a pH = 1 was reached with seeding at pH = 5−7. The final slurry was aged at 5 °C for 45 min, filtered, and washed with water. This solid *N*-Boc homoserine was then dried overnight in vacuo (26 Torr at 40 °C) with a nitrogen sweep giving 5.9 kg of *N*-Boc homoserine (80% yield). All spectral data matched authentic comercially available material.

***N*-Boc L-Homoserine Ethyl Ester (6).** To a slurry of *N*-Boc L-homoserine (4.55 kg, 20.8 mol) in THF (23 L) was added DBU (3.10 L, 20.8 mol) via an addition funnel (note: exothermic step, temperature must be maintained below 30 °C). Upon complete addition of DBU, iodoethane (3.24 L, 41.5 mol) was charged to the mixture via an addition funnel. The reaction is then stirred 20 h at room temperature or until complete as judged by HPLC. The

reaction mixture is then quenched by addition of water (11 L). The mixture was diluted with *i*-PrAc (23 L), and the organic layer was separated. The organic layer was washed with saturated aq $NaHCO_3$ (11 L) followed by water (11 L). The organics were then concentrated to a neat oil which may solidify upon standing, giving 4.52 kg of **6** (88% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.45 (br d, J = 6.4 Hz, 1H), 4.39 (br t, J = 8.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.66−3.61 (m, 2H), 3.38 (br s, 1H), 2.08−1.99 (m, 1H), 1.65−1.59 (m, 1H), 1.40 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 162.7, 156.5, 80.4, 61.6, 58.3, 50.8, 36.1, 28.3, 14.1. HRMS (ESI, NaOAc): exact mass calcd for $C_{11}H_{21}NO_5$ [M + Na], 270.1317. Found 270.1321.

(*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-butyric Acid Ethyl Ester (3b). The crude oil (or solid) *N*-Boc homoserine ethyl ester **6** (2.08 kg, 8.40 mol) was dissolved in CH_2Cl_2 (9 L) along with TEMPO (28 g, 179 mmol). This solution was allowed to stir at room temeprature while a bleach solution was prepared as follows: KBr (2.10 kg, 17.6 mol) was added to a 5.25 wt % aqueous bleach solution (47 L) followed by KH_2PO_4 (1.20 kg, 8.82 mol). The pH slowly will decrease from 11.6 to 9.5, then rapidly after pH 9. When pH has reached 7.8, the **6**/TEMPO solution in CH_2Cl_2 was added in a rapid manner, immediately followed by K_2HPO_4 (1.50 kg, 8.61 mol). The initially dark red solution became colorless in 5 min, and the pH will stablize at 6.5−6.8. At this point, if HPLC indicates remaining alcohol **6** or a pH = 5, then additional bleach may be added to complete conversion (an additional 47 L of 5.25 wt % bleach may be added as needed). When conversion was judged to be >99% by HPLC, the reaction was quenched by addition of $Na_2S_2O_3$ (2.80 kg, 17.7 mol). After stirring for 5 min, the organic phase was separated and the aqueous was extracted with CH_2Cl_2 (9 L). The combined organics were washed with sat aq $NaHCO_3$ (9 L), dried with $MgSO_4$, filtered, and concentrated to a yellow oil of 85 wt % aldehyde **3b** (1.44 kg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.74 (s, 1H), 5.38 (br d, J = 6.0 Hz, 1H), 4.60−4.56 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.11−2.98 (m, 2H), 1.45 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 170.9, 155.3, 80.1, 61.8, 48.7, 46.0, 28.2, 14.0. Exact mass calcd for $C_{11}H_{19}NO_5$ [M + Na], 268.1161. Found 268.1156.

(*Z*)-(*S*)-2-*tert*-Butoxycarbonylamino-5-cyano-(2,3-difluorophenyl)-pent-4-enoic Acid Methyl Ester (10a). To a solution of aldehyde **3b** (11.5 g at 88.3 wt %, 41.4 mmol) in 172 mL of THF was added 2,3-difluorophenylacetonitrile **2** (6.48 g, 42.3 mmol). After cooling to 0 °C, DBU (8.10 mL, 53.5 mmol) was added over 5 min. The ice bath was removed, and stirring was continued at room temperature for 4 h. After this time, iodomethane (5.55 mL, 89.1 mL) was added and the mixture was stirred for 20 h. The reaction mixture was then poured into a separatory funnel containing 150 mL of MTBE and 150 mL of 10% aq citric acid. The organic layer was then separated and washed with 100 mL of water followed by 100 mL of saturated aq $NaHCO_3$. The organics were then dried with Na_2SO_4, filtered, and concd in vacuo to a crude oil which was purified by column chromatography (gradient 17% to 25% EtOAc in hexanes). This gave 11.5 g of a 92 wt % oil (70% yield) of **10a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.07 (m, 3H), 6.89 (dd, J = 8.1, 7.4 Hz, 1H), 5.38 (br d, J = 7.8 Hz, 1H), 4.58−4.56 (br m, 1H), 3.77 (s, 3H), 3.16−3.08 (m, 1H), 3.01−2.92 (m, 1H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 155.2, 150.9 (dd, J_{CF} = 249.4, 13.1 Hz), 148.2 (dd, J_{CF} = 253.9, 13.6 Hz), 147.3 (d, J = 7.0 Hz), 124.6 (dd, J_{CF} = 7.0, 5.0 Hz), 124.3 (d, J = 3.0 Hz), 123.4 (d, J = 8.0 Hz), 118.0 (d, J = 17.1 Hz), 115.2, 112.3, 80.4, 52.8, 52.5, 36.1, 28.2. Exact mass calcd for $C_{18}H_{20}F_2N_2O_4$ [M + Na], 389.1289. Found 389.1294. Assay of enantiomeric excess: HPLC analysis (Chiralpak AD-H, 5% IPA/heptane, 1 mL/min, 30 °C, 210 nm; t_r (minor isomer) = 13.4, t_r (major isomer) = 15.8), 99.0% ee.

(*Z*)-(*S*)-2-*tert*-Butoxycarbonylamino-5-cyano-(2,3-difluorophenyl)-pent-4-enoic Acid Ethyl Ester (10b). A 75 L round-bottomed flask was charged with THF (27 L) and LiHMDS (1 M in THF, 13.1 L, 13.1 mol). The solution was cooled to −45 °C, and 2,3-difluorophenylacetonitrile **2** (1.66 kg, 10.8 mol) was added over 10 min. The reaction mixture was stirred at −35 °C for 15 min, then a solution of the aldehyde **3b** (2.80 kg, 11.4 mol) in THF (10 L) was added over 10 min while maintaining the temperature below −30 °C. After the addition, the reaction mixture was treated with MsCl (2.48 kg, 21.7 mol) and Et_3N (2.74 kg, 27.1 mol). The reaction was allowed to warm to room temperature and stirred for 2−3 h. This was then quenched into a mixture of MTBE (40 L) and 10 wt % citric acid solution (35 L). The aqueous layer was removed, and the organic layer was washed with 5% $NaHCO_3$ (30 L), brine (5%, 30 L), dried with $MgSO_4$, filtered, and concentrated in vacuo to a 74 wt % crude oil of **10b** (3.10 kg, 8:1 *Z*:*E*, 99% ee, 75% yield). This material is further purified by column chromatography (gradient 5% to 25% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.09 (m, 3H), 6.92 (t, J = 7.8 Hz, 1H), 5.32 (br d, J = 6.5 Hz, 1H), 4.58−4.56 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.18−3.12 (m, 1H), 3.05−2.97 (m, 1H), 1.43 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 155.1, 150.9 (dd, J_{CF} = 249.7, 12.8 Hz), 148.1 (dd, J_{CF} = 253.9, 14.1 Hz), 147.3 (d, J = 7.1 Hz), 124.5 (dd, J_{CF} = 6.9, 5.2 Hz), 124.3 (d, J = 3.4 Hz), 123.3 (d, J = 8.3 Hz), 118.0 (d, J = 17.4 Hz), 115.2, 112.2, 80.3, 62.1, 52.4, 36.2, 14.1. Exact mass calcd for $C_{19}H_{22}F_2N_2O_4$ [M + Na], 403.1445. Found 403.1450. Assay of enantiomeric excess: HPLC analysis (Chiralpak AD-H, 5% IPA/heptane, 1 mL/min, 30 °C, 210 nm; t_r (minor isomer) = 12.9, t_r (major isomer) = 14.5), 99.3% ee.

Typical Procedure for Nitrile Hydrogenation. [(*S*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-yl]-carbamic Acid *tert*-Butyl Ester (1). A high-pressure reaction vessel was charged with 1 equiv of either methyl ester **10a** or ethyl ester **10b** dissolved in 20 mL/g of methanol followed by 1.5 equiv of triethylamine. The vessel was then charged with 100−150 wt % of methanol washed Raney-Co 2724. The mixture was then heated to 40 °C under 450 psi of hydrogen for 8 h. The mixture was filtered through a pad of celite with methanol and concentrated in vacuo. The crude oil **1** may then be purified directly by column chromatography (60% EtOAc in hexanes). Alternatively, the crude oil **1** can be purified by diluting with EtOAc (20 mL/g) and washing with 1 N HCl (2 × 12.5 mL/g), water (12.5 mL/g), saturated aq $NaHCO_3$ (12.5 mL/g), and brine (12.5 mL/g). Then the organic layer is dried with Na_2SO_4, filtered, and concentrated in vacuo. Further purification can be achieved by removal of the Boc-moiety and crystallization of the HCl salt (addition of 5 equiv of dry HCl in IPA to a solution of **1** in ethanol at 40 °C for 4 h gives crystalline solid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13−7.01 (om, 3H), 6.93 (m, 1 H), 6.42 (br t, J = 6.0 Hz, 1 H), 5.88−5.87 (m, 1H), 5.80 (br d, J = 6.0 Hz, 1H), 5.07−5.01 (m, 1H), 4.59 (br d, J = 17.7 Hz, 1H), 3.66 (dd, J = 17.5, 7.6 Hz, 1H), 2.95−2.89 (m, 1H), 2.46−2.38 (m, 1H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 155.2, 151.4 (dd, J_{CF} = 249.0, 12.8 Hz), 147.6 (dd, J_{CF} = 124.0, 13.0 Hz), 132.8, 132.3 (d, J = 11.7 Hz), 130.9, 124.3 (m, 2C), 116.5 (d, J = 8.6 Hz), 79.9, 49.3, 43.1 (d, J = 5.1 Hz), 33.5, 28.4. Exact mass calcd for $C_{17}H_{20}F_2N_2O_3$ [M + Na], 361.1340. Found 361.1342. Melting point of 8% ee solids 202.8−206.2 °C. Assay of enantiomeric excess: SFC analysis (Chiralpak AD-H, 20% (25 mM *i*-$BuNH_2$ in MeOH)/CO_2, 1.5 mL/min, 200 bar, 35 C; t_r (isomer 1) = 6.1, t_r (isomer 2) = 7.4), 80−90% ee.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C spectra for compounds **1**, **10a**, **10b**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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