

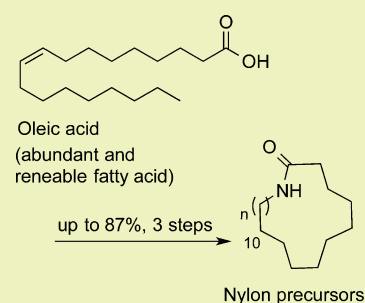
Simple Ring-Closing Metathesis Approach for Synthesis of PA11, 12, and 13 Precursors from Oleic Acid

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Supporting Information

ABSTRACT: Due to the concerns over limited fossil resources and increasing CO₂ emissions, there is a strong interest in use of renewable resources in production of valuable synthetic materials. PA11, 12, and 13, more commonly known as Nylon, are high-strength polymers that find use in various industrial sectors. They are traditionally produced from petroleum-derived material or exotic fatty acids using reaction sequences that involve 4–6 steps. Herein we report a simple three-step synthesis of these polyamide precursors from oleic acid, an abundant natural fatty acid available from common plant sources as well as oleaginous micro-organisms such as microalgae. This approach represents the first example where ring-closing metathesis was used for the key C–C bond forming step, featuring introduction of amine functionality required in the final product. Our versatile approach allows preparation of nylon precursors of various chain-lengths from a single starting material for economical and sustainable production of these polymers.

KEYWORDS: Synthetic methods, green chemistry, olefin metathesis, oleic acid, nylon 12, PA12, nylon, PA



INTRODUCTION

Concerns over depleting fossil resources and increasing CO₂ emissions have invigorated research seeking alternative pathways for production of commodity-scale materials traditionally manufactured from petroleum resources. Such alternatives should preferably utilize renewable feedstocks (e.g., biomass) while remaining environmentally and economically sustainable.^{1–4} Progress in this field is particularly important for polymer manufacturing because of the increasing economic and environmental impact of these products due to their growing use and production.⁵

Linear chain polyamides with a general formula $-\text{[(CH}_2\text{)}_n\text{-CONH]}_m\text{-}$ or $-\text{[(CH}_2\text{)}_n\text{-CONH-(CH}_2\text{)}_m\text{NHCO]}_m\text{-}$, commonly known as Nylon, are one of the most widely used classes of polymers. They are named with a prefix PA followed by the number of carbons separating amide bonds in the carbon chain. PA11, 12, and 13 are high-strength materials that have found use across many industrial sectors. These polymers are produced by polymerization of linear or cyclic amino acid precursors (Figure 1, 1–4).

The precursor of PA12, lactam **1**, is currently manufactured from petroleum resources in six steps (Figure 1a).^{6–8} In fact, there was a serious shortage in these polyamides in 2012 due to a safety related closure of one of the manufacturing facilities that produced petroleum-based intermediates.⁹ The incident accelerated a search for alternative materials or synthetic routes for these high-value polymers. The synthesis of PA11 and 12 precursors from plant-derived fatty acids has been repor-

ted;^{8,10–15} however, they involve multiple steps (4–6 steps) and use ricinoleic acid, a fatty acid available naturally only from castor beans, or other uncommon fatty acids, as the starting material (Figure 1c).^{11,16–32}

One of the strategies used in these methods involve cross-metathesis (CM) of fatty acids with functional olefins to give bifunctional products.^{13,26} However, because of the incompatibility of amino group to metathesis,³³ this functional group was first introduced in the form of nitrile during metathesis and subsequently converted to amine through energy-intensive hydrogenation.^{24–26,34} Alternatively, the amino group has been introduced at a downstream step, but this increases the overall number of synthetic steps. In addition, some CM strategies require multiple equivalents of reagents and/or separate self-metathesis steps to achieve good selectivity in cross coupling.³⁰ Some CM reactions cause undesirable isomerization during CM that reduces the overall yields—the problem that is particularly significant when nonconjugated nitriles are used.^{17,35} It is likely that other syntheses have resorted to use of uncommon fatty acids to circumvent some of the issues associated with low yields from CM of oleic acid to PA12 and 13 precursors.³⁵

Herein, we report a ring-closing metathesis (RCM) approach that allows the use of oleic acid (**5**), a natural fatty acid available

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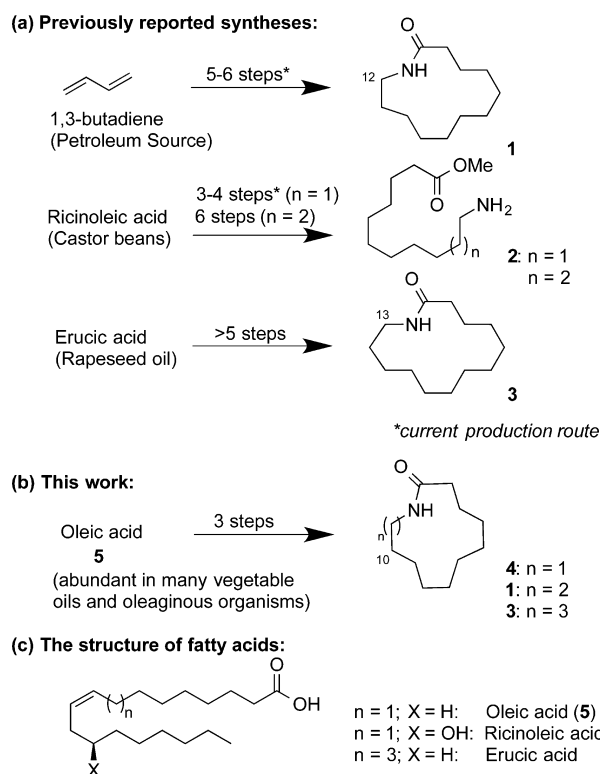


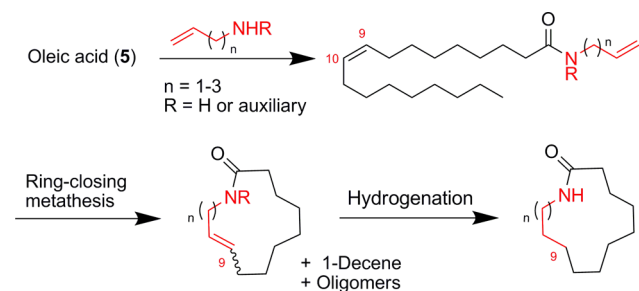
Figure 1. (a) Previously reported syntheses of nylon 11–13 precursors involve multiple steps and require either petroleum feedstock or uncommon fatty acids. (b) Three-step synthesis of the same precursors from oleic acid reported herein. (c) Structures of the natural fatty acids.

from common plant sources, as well as oleaginous microorganisms, including microalgae^{36–39} (Figure 1b), as a unified platform molecule for synthesis of PA11, 12, and 13 precursors. Our approach features direct introduction of amine group, thereby avoiding energy-intensive nitrile hydrogenation. Moreover, this approach is less susceptible to undesirable isomerization or self-metathesis, which complicates the isolation of the final material. Our study represents the first example of the use of RCM to generate nylon precursors from fatty acids.

RESULTS AND DISCUSSION

Our general strategy for PA11–13 precursors involves three steps (Scheme 1). First, oleic acid is converted to alkenyl amides, which are then subjected to RCM,³³ generating unsaturated ene-lactams. They are subsequently hydrogenated to saturated lactams, the precursors for PA12 and 13

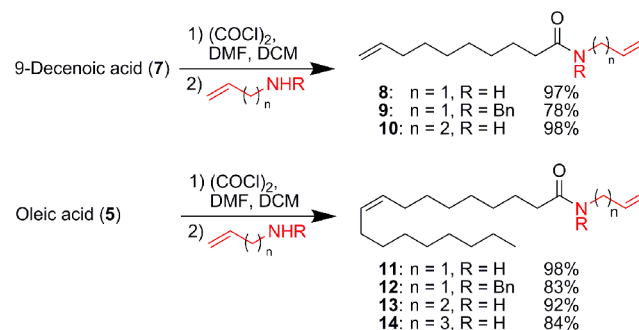
Scheme 1. General Strategy from Oleic Acid to Nylon Precursors



production. The precursor for PA11 preparation is a linear amino ester, which can be readily accessed by solvolysis of the lactam. Thus, the proposed method utilizes various amines with terminal olefins to adjust the carbon length of the final product.^{40–43}

We synthesized several amides from 9-decenoic acid and oleic acid as part of our investigations (Scheme 2). A conventional method using acid chlorides provided the desired amides in 78–99% yields.

Scheme 2. Amide Formation from 9-Decenoic Acid (Model Compound) and Oleic Acid



The examination for RCM was initiated with model amide 10. Under the typical reaction conditions using Hoveyda-Grubb's second-generation catalyst,^{33,44} the reaction successfully generated the ene-lactam 15 in ~60% by gas chromatography (GC) analysis (Table 1, entry 2); various other reaction conditions were also examined in order to improve yields (Table 1). To compensate for catalyst deactivation at high temperatures, a catalyst was added to the reaction mixture over a period of time such that overall catalyst

Table 1. Ring-Closing Metathesis Optimization from 10 to 15^a

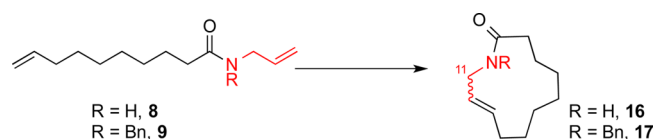
entry	conc. (mM)	catalyst (mol %)	time (h)	temp. ^b (°C)	conv. ^c (%)	15 ^c (%)
1	4	1	7	110	64	28
2	4	1	5	90	70	60
3	4	2	5	90	90	68
4	2	2	2	90	95	79
5	4	2	7	80	99	51
6	2	2	8	80	94	42
7	2	5	4	90	93	75
8	2	3	4	90	97	79
9 ^d	2	2	4.5	90	79	25
10	2	5	2.5	100	97	80
11	2	2	2.5	100	97	73
12 ^e	2	2	2	90	92	78
13 ^f	2	2	2	90	94	70

^aReaction conditions: Hoveyda-Grubbs second generation catalyst in toluene (1 mL) was charged into a solution of 10 in toluene over 1 h at the indicated temperatures. ^bOil bath temperature. ^cGC area%. ^dWith 5 mol % of $\text{Ti}(\text{O}i\text{Pr})_4$. ^eChlorobenzene was used. ^fAnisole was used.

activity was maintained during the reaction. We found that a catalyst addition time of >1 h gave optimal reaction conversion under otherwise identical conditions (not shown). Minimally, 2 mol % catalyst was required under these conditions (entries 1, 2 vs 3, 4 vs 7 and 8, 10 vs 11). Higher temperatures were preferred for the reactions because greater formation of oligomers was observed at lower temperatures, which reduced the yield of desired product (entries 6 vs 4 and 11).^{45,46} It was found that the concentration of the substrate also had a large effect on the reaction progress (entries 3 vs 4) and higher yields were observed in reactions under more dilute reaction conditions. Addition of Ti(OiPr)₄, a Lewis acid reported to suppress undesired chelation to allyl ester,¹ was not effective for amide **10** (entry 9). Finally, among the three solvents screened (toluene, anisole and chlorobenzene), chlorobenzene gave the cleanest product profile while maintaining good reaction conversion (entries 4, 12 and 13).

Contrary to our expectations, amide **8**, the precursor for C11 lactam (**4**), did not yield any desired product under the RCM conditions optimized for amide **10** (Table 2). No ene-lactam

Table 2. Ring-Closing Metathesis Optimization from **8 to **16** and **9** to **17**^a**



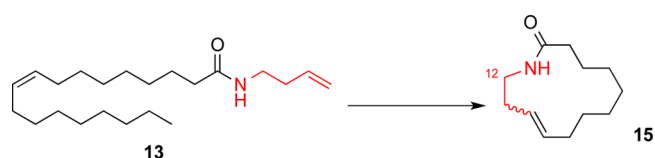
entry	R	conc. (mM)	catalyst (mol %)	time (h)	temp. ^b (°C)	conv. ^c (%)	16/17 (%)
1	H	10	1	17	110	44	0
2	H	10	5	6	110	69	0
3	H	4	2	2	110	22	0
4	H	0.5	2	6	110	70	0
5	H	4	2	7	110	64	0
6	H	2	5	2.5	90	22	0
7 ^d	H	2	2	5	90	30	0
8	Bn	2	2	2	90	74	34
9	Bn	2	2	2	90	73	44

^aReaction conditions: Hoveyda-Grubbs second generation catalyst in chlorobenzene (1 mL) was charged into a solution of **10** in chlorobenzene over 1 h at the indicated temperatures. ^bOil bath temperature. ^cGC area%. ^dWith 5 mol % of Ti(OiPr)₄.

formation was seen at any temperature, catalyst loading, substrate concentration, or with a Lewis acid additive¹ (entries 1–7). With the notion that attaching a substituent on amide should improve the macrocyclization by facilitating the required *s-cis* conformation for the ring closure,^{33,47,48} RCM of *N*-benzyl amide **9** was investigated. We selected benzyl group with the expectation that it could be removed during the final hydrogenation step (Scheme 1). We were pleased to find that amide **9** underwent the desired cyclization, giving ene-lactam **10** in moderate yields (entries 8–9).

After gaining insight into reaction conditions from experiments with model compounds, we proceeded to examine the amides prepared from oleic acid (Scheme 2, amides **11**–**14**). In general, these amides showed better reactivity and selectivity toward RCM than the respective model substrates (Tables 1 vs 3 and 2 vs 4). This observation may be attributed to the lower reactivity of internal olefin (relative to terminal olefin) that suppresses the undesired oligomerization.

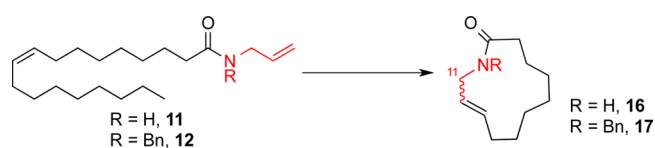
Table 3. Ring-Closing Metathesis Optimization from **13 to **15**^a**



entry	conc. (mM)	temp. ^b (°C)	time (h)	conv. ^c (%)	15 (%)	oligomers ^c (%)
1	2	90	2	94	43	19
2	2	90	1	92	39	22
3	3	90	2	93	46	10
4 ^d	2	90	1	97	47	4
5	20	90	1	92	19	22
6	10	90	1	96	22	14
7	2	100	1	95	60	20
8	2	110	1	96	64	16
9	2	120	1	95	66	15
10 ^d	2	120	0.5	97	71	10
11 ^d	2	120	0.25	96	70	11
12 ^d	4	120	0.25	93	58 (87) ^e	15

^aReaction conditions: Hoveyda-Grubbs second generation catalyst in chlorobenzene (1 mL) was charged into a solution of **10** in chlorobenzene over 1 h at the indicated temperatures. ^bOil bath temperature. ^cGC area%. ^dThe catalyst charged in one portion at the reaction start. ^eIsolated yield (corrected for its purity).

Table 4. Ring-Closing Metathesis Optimization from **13 to **15**^a**



entry	R	time (h)	temp. ^b (°C)	conv. (%)	16/17 ^c (%)	oligomers (%) ^c
1	H	22	110	39	16	13
2	Bn	1	110	84	61 (52) ^d	12
3	Bn	2	120	94	68 (53) ^d	12

^aReaction conditions: Hoveyda-Grubbs second generation catalyst in chlorobenzene (1 mL) was charged into a solution of **10** in chlorobenzene over 1 h at the indicated temperatures. ^bOil bath temperature. ^cGC area%. ^dIsolated yield.

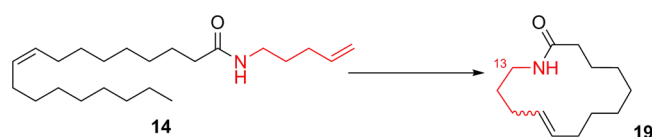
First, RCM of amide **13** for the production of PA12 precursor was studied under various reaction conditions (Table 3). We found that the reaction completes much faster and slow catalyst addition was no longer necessary (entries 10–12). The formation of lactam **15** was higher at elevated temperature, the same phenomenon we observed with amide **10** (entries 2, 7–9). The effect of concentration of the reaction mixture was also investigated, higher concentration gave slightly better reaction conversion; however, competing oligomerization became predominant (entries 2, 3, 5 and 6). We found that a 2 mM concentration showed the best balance of conversion and selectivity. We were pleased to find that under the optimal reaction conditions, an excellent yield of the desired ene-lactam **15** was obtained (entry 12).

Next, RCM of amides **11** and **12** was investigated (Table 4). As before, an increased reactivity was seen with these amides to those derived from 9-decanoic acid. A small amount of the desired ene-lactam **16** was seen when the nonprotected amide

11 was subjected to RCM conditions (entry 1). As seen with model amide 9, *N*-protected amide 12 gave a better conversion. Thus, a good yield of lactam 17 was isolated under the optimized reaction conditions used for lactam 15.

Finally, amide 14 was examined for RCM under several reaction conditions (Table 5). The reaction gave over 90%

Table 5. Ring-Closing Metathesis Optimization from 18 to 19^a



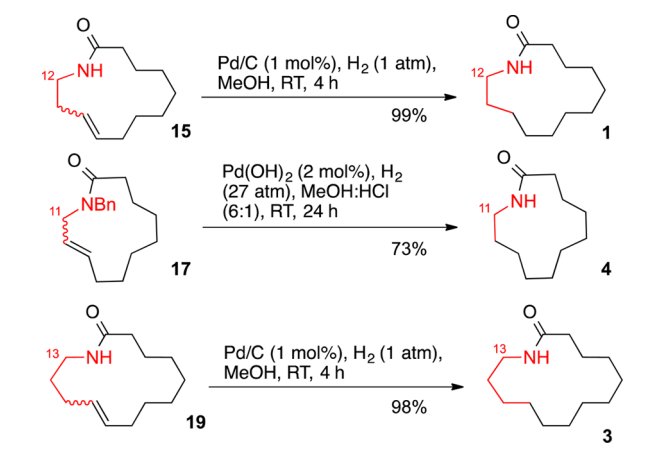
entry	conc. (mM)	time (h)	temp. ^b (°C)	conv. ^b (%)	19 ^c (%)	oligomers ^c (%)
1	3	2	110	92	56 (83) ^f	21
2 ^d	4	0.25	120	93	43	24
3 ^e	2	2	110	94	49	21
4	2	2	90	93	42	21

^aReaction conditions: Hoveyda-Grubbs second generation catalyst (2 mol %) in chlorobenzene (1 mL) was charged into a solution of 10 in chlorobenzene over 1 h at the indicated temperatures. ^bOil bath temperature. ^cGC area%. ^dThe catalyst was charged in one portion at the reaction start. ^e1 mol % of the catalyst was used. ^fIsolated yield.

conversion under all the conditions tested. As before, oligomer formation was (comparatively) suppressed at higher temperature showing a better selectivity toward cyclization (entries 4 vs 1 and 3). With this substrate, slow addition of catalyst was necessary to achieve good selectivity (entry 2). Under the optimal conditions, excellent yield of the desired ene-lactam 19 was obtained (entry 1).

Completion of the synthesis was achieved by hydrogenation of the ene-lactams 15, 17 and 19, providing lactams 1, 4 and 3, respectively (Scheme 3). Hydrogenation of lactams 15 and 19

Scheme 3. Hydrogenation of ene-Lactams to Saturated Lactams (Nylon 11–13 Precursors)



was accomplished by using a Pd/C catalyst at ambient temperature and pressure, giving quantitative yields of the desired lactams. Use of residual Hoveyda-Grubbs catalyst for tandem metathesis-hydrogenation^{25,49–51} was also examined; however, this required high-pressure in our system. The simultaneous removal of the benzyl group of lactam 17 was

also achieved using Pearlman's catalyst under 27 atm pressure of hydrogen in acidic media, to give 73% yield of lactam 4.

CONCLUSION

In conclusion, we have established a three-step synthesis of precursors of PA11, 12 and 13 from the abundantly available and renewable oleic acid. Our study represents the first approach that uses RCM for the key C–C bond formation in polyamide precursors, featuring direct introduction of amino group that was not possible with the CM approach.¹³ Each step was optimized, resulting in good overall yield, particularly for PA12 precursor synthesis (82%, three steps). The versatility of our approach not only allows preparation of precursors of PA11–13 but also provides new avenues to economically and sustainably access polyamide precursors with longer carbon-chains from the same starting material. Studies directed toward application of continuous process, isolation method amenable on scale,⁵² as well as polymerization of the lactams, are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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