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A Concise, metathesis based approach to construction of the lepadiformine/cylindricine tricyclic framework

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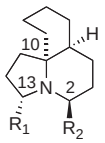
ABSTRACT

A tandem dienyne metathesis based strategy has been developed for construction of the core tricyclic framework found in the lepadiformine and cylindricine alkaloids. 2-Pentenyl-2-ethynylpyrollidine acrylamide that serves as the starting material for the key ruthenium carbene catalyzed metathesis process is prepared by using a concise route starting with L-proline.

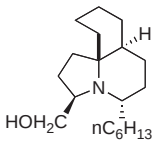
1. Introduction

The lepadiformines are structurally interesting alkaloids isolated from the marine organisms *clavelina lepadiformis* and *clavelina moluccensis* by Biard and his co-workers.[1–3] Members of this family share a common tricyclic-amine skeleton but differ in the nature of substituents at the C-2 and C-13 positions. Lepadiformine A, the first member of this family that was isolated and characterized,[1,2] possesses a C-2 *n*-hexyl and C-13 hydroxymethyl moiety. In contrast, *n*-butyl and hydroxymethyl groups are located at the respective C-2 and C-13 centers in lepadiformine B, and lepadiformine C contains a C-2 *n*-butyl group but lacks substitution at C-13.[3] Interestingly, these alkaloids have tricyclic structures and substituent patterns that closely resemble those found in members of the cylindricine alkaloid family (e.g., cylindricine B).[4] One of the major differences between the lepadiformines and cylindricines are the configurations at the side chain bearing C-2 and C-13 carbons and the quaternary C-10 carbon.



lepadiformines

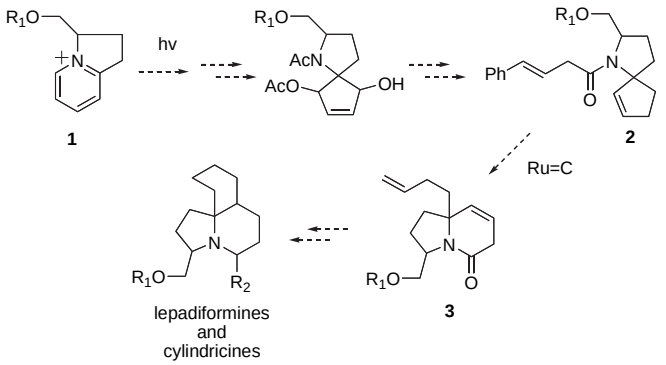
A (R_1 = CH_2OH, R_2 = nC_6H_{13})
B (R_1 = CH_2OH, R_2 = nC_4H_9)
C (R_1 = H, R_2 = nC_4H_9)



cylindricine B

Lepadiformine A and the cylindricines attracted interest in the synthetic community beginning shortly after their isolation in the mid 1990s.[5,6] The varied strategies that have been used to prepare these targets rely on a broad array of modern synthetic methodologies. Recently, synthetic approaches to lepadiformine A and the cylindricines have been thoroughly reviewed by Weinreb.[7]

The results of our earlier studies in the area of pyridinium salt photochemistry[8,9] provide the foundation for a new, photochemical strategy to construct the tricyclic skeleton of the lepadiformines and cylindricines. At the beginning of studies in this area, we envisaged that the spirocyclic *N*-butenamidocyclopentene **2** could be accessed by employing a route that involves documented sequential photocyclization-aziridine ring opening,[9] starting with the cyclopenta-fused pyridinium perchlorate **1** (Scheme 1). Furthermore, we hypothesized that ring rearrangement metathesis of the spirocyclic



Scheme 1.

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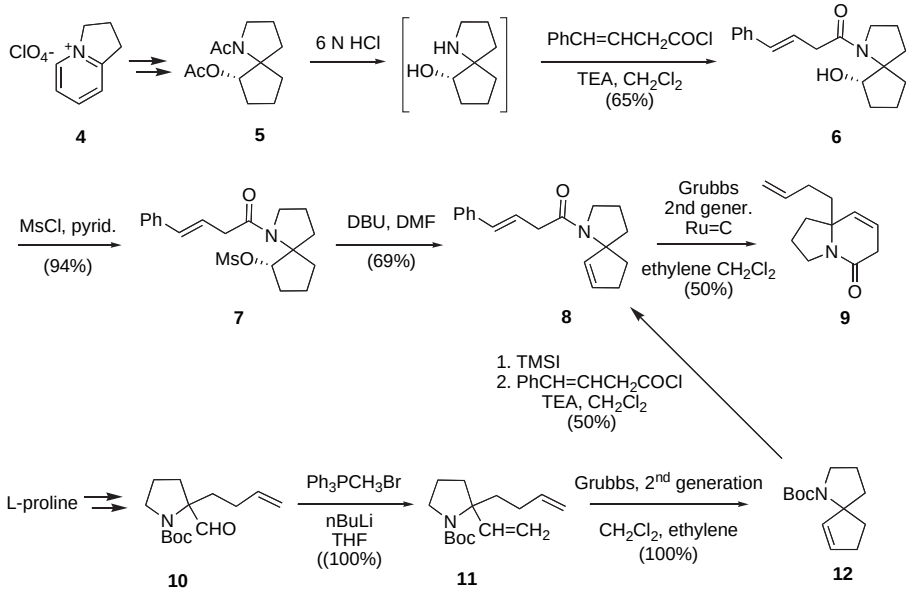
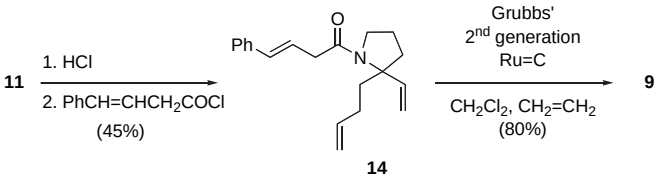
butenamide **2** would produce the indolizidine **3**,[10] which contains a properly positioned four-carbon side chain needed for construction of the final six-membered ring in the tricyclic framework that constitutes the backbone of the target alkaloids.

In order to test this approach, the model spirocyclic amide **5** (Scheme 2) was prepared in racemic form by using either a photochemical route, starting with pyridinium salt **4**,[9] or a metathesis based method[11,12] beginning with L-proline (Scheme 2). Treatment of an ethylene saturated CH_2Cl_2 solution of **8** with the second generation Grubbs' ruthenium catalyst[13,14] did promote tandem ring opening–ring closing metathesis[15,16] to produce the indolizidine **9** in modest yield.



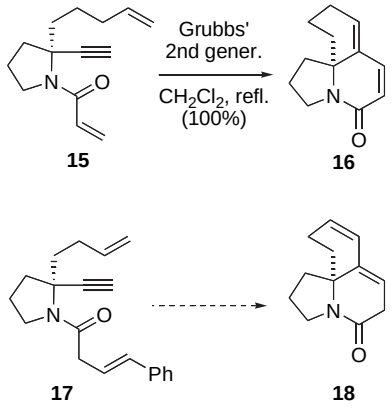
Scheme 2.

At this point, potentially more efficient strategies for construction of the tricyclic core structures of the lepadiformine and cylindricine alkaloids became apparent. For example, we recognized that an alternate approach existed for the preparation of indolizidine **9** involving early introduction of the butenoyl-amide side chain. This expectation proved to be correct as demonstrated by the high yielding (80%) conversion of the pyrrolidine triene **14**, generated from the known[11] Boc-protected pyrrolidine **11**, to indolizidine **9** promoted by treatment with the second generation Grubbs' catalyst in the presence of ethylene (Scheme 3). It should be noted that the mechanistic pathway for this process must involve ruthenium alkylidene formation involving either the styryl or vinyl double bond. Alternative routes via formation and cyclization of the side chain butenyl derived ruthenium alkylidene would lead to formation of highly strained five- or eight-membered rings.

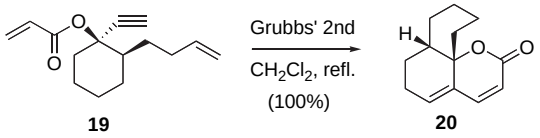


Scheme 3.

The final iteration in the development of a highly concise strategy for construction of the lepadiformine/cylindricine tricyclic skeleton came from the belated recognition that the 2-ethynyl-2-pentenylpyrrolidine acrylamide **15** and/or the analogous 2-ethynyl-2-butenylpyrrolidine butenamide **17** could be prepared in enantiomerically pure forms by using short routes starting with either D- or L-proline. Moreover, we anticipated that treatment of **15** and/or **17** with a Grubbs' ruthenium carbene catalyst could promote dienyne metathesis[17–19] to produce the respective tricyclic dienamides **16** and **18** (Scheme 4). This expectation was based on the results of earlier work by Choi and Grubbs,[20] which showed that the substituted cyclohexyl ester **19** undergoes highly efficient conversion (100%) to the tricyclic-lactone **20** when treated with the second generation Grubbs catalyst (Scheme 5). In addition, dienyne metathesis has been employed in novel approaches to the synthesis of securine[21] and members of the erythrina alkaloid family.[22–24]



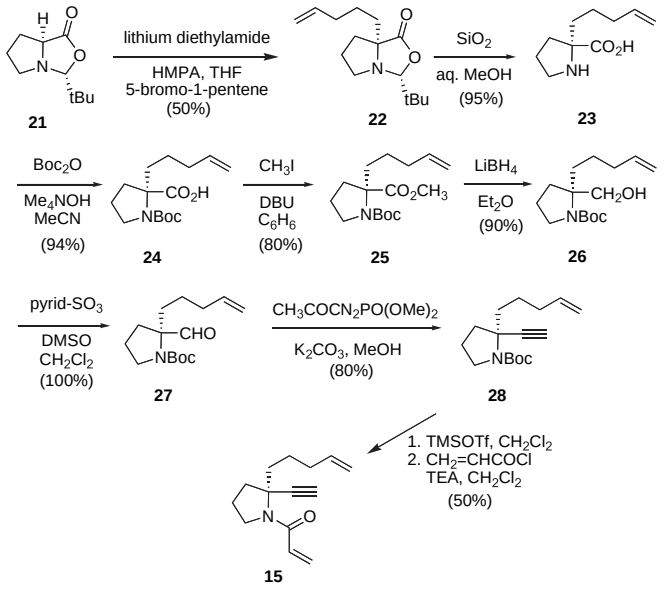
Scheme 4.



Scheme 5.

The feasibility of these metathesis based strategies was tested in the context of applications to the preparation of the tricyclic dienamides **16** and **18**. Following the methodology prescribed by

Seebach[25] and others,[26–28] L-proline was sequentially transformed to the (*S*)-2-pentenyl derivative **22** via alkylation of the known[25] bicyclic-oxazolidinone **21** (Scheme 6). By using methodology developed by Bestmann,[29] aldehyde **27** was converted to corresponding Boc-protected 2-pentenyl-2-ethynyl pyrrolidine **28**. Finally, deprotection of **28** followed by acrylamide formation gave the key dienyne **15**.

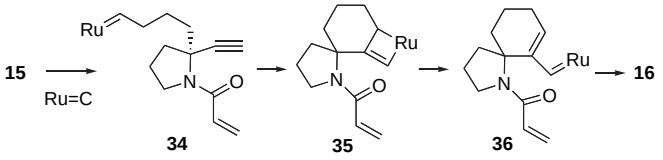


Scheme 6.

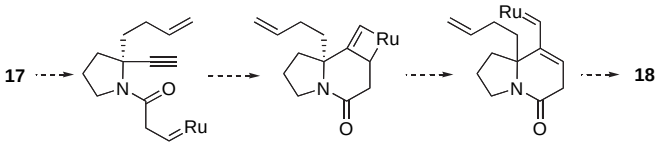
The butenamide **17** was prepared via a sequence that begins with the known[26] carboxylic acid **29** (Scheme 7). Conversion of this substance to aldehyde **32** followed by installation of the alkyne moiety provides the protected pyrrolidine derivative **33**, which is transformed to **17** by deprotection and amide formation.

In the anticipated manner, the pentenyl-acrylamide **15** undergoes clean dienyne metathesis to generate the tricyclic dienamide **16** (Scheme 4). The best conditions for performing this process involve refluxing CH_2Cl_2 and the Grubbs second generation ruthenium catalyst. In this way, **15** is transformed to the tricyclic dienamide **16** in yields as high as 100%. Surprisingly, conducting the ring closing metathesis (RCM) process on an ethylene saturated solution of **15** under otherwise identical conditions leads to formation of a complex product mixture. In contrast, treatment of the butenyl-butenamide **17** under a variety of reaction conditions (e. g., room temperature-to-refluxing CH_2Cl_2, with and without ethylene) failed to promote formation of the tricyclic dienamide **18**. Moreover, no identifiable products could be isolated from the complex mixtures that are produced in these processes.

Borrowing from the mechanistic reasoning provided by Choi and Grubbs,[20] the conversion of **15** to **16** likely involves preferential addition of the initially formed, pentenyl double bond derived ruthenium alkylidene **34** to the acetylene moiety rather than the acrylamide group. This process provides an intermediate ruthenocyclobutene **35**, which undergoes sequential electrocyclic ring opening to form the rutheno-vinylcyclohexene **36** and RCM with the acrylamide alkene moiety to form **16** (Scheme 8). Although any explanation for the lack of dienyne metathesis reactivity of **17** is speculative at this point, it should be noted that the success of this process requires that initial ruthenium alkylidene formation take place at the styryl group (Scheme 9). In another route involving ruthenium alkylidene formation at the butenyl double bond, cyclization would produce strained five- and eight-membered ring systems.

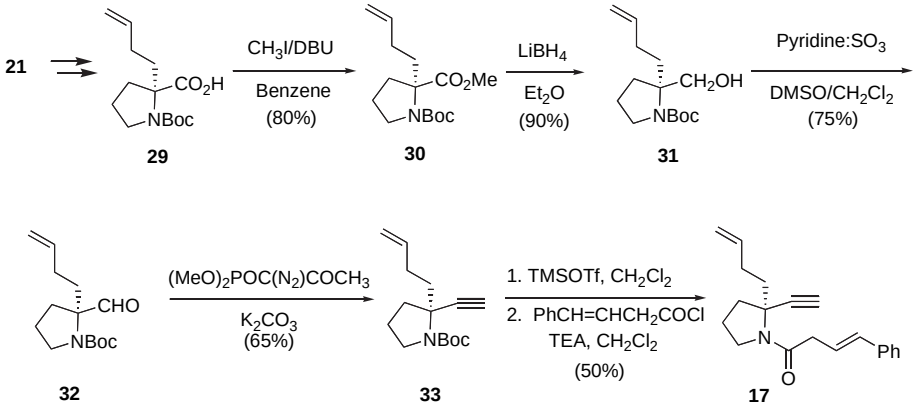


Scheme 8.



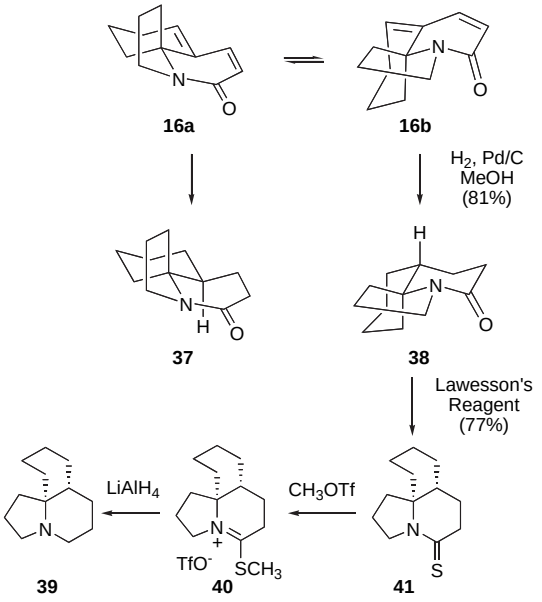
Scheme 9.

In addition to an early incorporation of a hydroxymethyl group that would be ultimately positioned at C-13 in the tricyclic skeletons of the targets,[30] completion of either a lepadiformine or cylindricine synthesis by using dienyne metathesis based routes requires methodology for stereocontrolled reduction of the C-5,C-6-double bond in dienamide **16** (or a hydroxymethyl analog) and the installation of a requisite alkyl chain at C-2. The former issue was briefly explored. Inspection of energy-minimized structures of **16** gives little indication that a preference exists between conformations **16a** and **16b** (Scheme 10). In conformer **16a**, the pyrrolidine ring is positioned to block Pd-complexation from the β-face of the γ,δ-alkene moiety while in **16b** the β-face of the alkene group is more accessible. We believed that, in accordance with this prediction, treatment of **16** with Pd/H_2 would result in the formation of a mixture of tricyclic lactams **37** and **38**, having the C-5 C-10



Scheme 7.

relative stereochemistry found in the respective lepadiformine and cylindricine alkaloids. However, in a manner, that is, contradictory to this expectation, catalytic hydrogenation of **16** affords the tricyclic lactam **38** exclusively, as shown by X-ray crystallographic analysis of the derived thiolactam **41** (see Supplementary data). In addition, **41** was converted to the known[31,32] tricyclic amine **39** through a pathway involving formation and $LiAlH_4$ reduction of the thioiminium salt **40**.



Scheme 10.

The study described above has led to the development of an efficient approach for construction of the tricyclic structural core shared by members of the lepadiformine and cylindricine alkaloid families. The key tricyclic dienamide **16** (or a hydroxymethyl analog), generated by using a highly efficient dienyne metathesis process, contains an array of functionality that could prove beneficial in synthesis of specific target in these natural product families.

2. Experimental

2.1. General

All reagents were obtained from commercial sources and used without further purification. All compounds were isolated as oils and shown to be >90% pure by ^1H and/or ^{13}C NMR analysis, unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded by using $CDCl_3$ solutions and with residual $CHCl_3$ was used as a reference.

2.1.1. Compound ***7****.* A solution of the known[33] amido-ester **5** (1.0 g, 4.5 mmol) in 6 N HCl (20 mL) was stirred at 100 °C for 3 h, cooled, and concentrated in vacuo to afford the spirocyclic aminoalcohol. Dry methylene chloride, triethylamine, and *trans*-styrylacetyl chloride (made from *trans*-styrylacetic acid (0.87 g, 5.4 mmol) and thionyl chloride (20 mL) at reflux for 3 h) were added sequentially and the resulting mixture was stirred overnight at room temperature, diluted with methyl chloride and water, washed with saturated aq sodium bicarbonate, dried, and concentrated in vacuo to yield a residue, which was subjected to column chromatography (30% acetone/hexane) on silica gel to provide the modestly unstable amido-alcohol **6** (0.83 g, 65%). ^1H NMR 1.45 (m, 2H),1.73 (m, 1H), 2.03 (m, 4H), 1.91 (m, 6H), 2.72 (m, 1H), 3.26 (m, 2H), 3.58 (m, 2H), 3.76 (m, 1H), 4.67 (m, 1H), 6.34 (m, 1H), 6.45 (m, 1H), 7.10–7.50 (m, 5H); ^{13}C NMR 21.1, 23.1, 34.5, 35.3, 40.3, 41.2, 49.4, 74.3, 81.7, 122.5, 126.2, 127.4, 128.4, 132.7, 136.8, 172.7. The modestly unstable nature of **6** prevented the attainment of HRMS data.

To a solution of amido-alcohol **6** (0.5 g, 1.8 mmol) and pyridine (1 mL) in dry methylene chloride (20 mL) at 0 °C was added methanesulfonyl chloride (0.67 g, 3.5 mmol). The mixture was stirred overnight at room temperature, diluted with methylene chloride and saturated aq sodium bicarbonate, separated, dried, and concentrated in vacuo to afford a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to provide **7** (0.60 g, 94%). ^1H NMR 1.49 (m, 2H), 1.86 (m, 2H), 2.03 (m, 4H), 2.38 (m, 1H), 2.93 (m, 4H), 3.25 (m, 2H), 3.62 (m, 2H), 4.66 (m, 1H), 6.43 (m, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR 22.0, 22.8, 32.8, 34.7, 38.6, 40.6, 41.5, 49.2, 71.1, 86.7, 123.4, 126.2, 127.3, 128.4, 132.7, 137.1, 170.2; HRMS (ES) *m*/*z* 364.1583, calcd for $C_{19}H_{26}NO_4S$ 364.1569.

2.1.2. Compound ***8*** *from* ***7****.* A solution of **7** (0.4 g, 1.1 mmol) and DBU (5 mL) in DMF (10 mL) was stirred at 120 °C for 12 h, cooled, and diluted with ethyl acetate, washed with saturated aq sodium chloride, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to provide **8** (0.2 g, 69%). ^1H NMR 1.1–1.5 (m, 3H), 1.7–2.0 (m, 4H), 2.2–2.8 (m, 2H), 3.2–3.6 (m, 3H), 5.52 (d, 0.5H), 5.71 (d, 0.5H), 5.84 (d, 0.5H), 5.90 (m, 0.5H), 7.1–7.5 (m, 6H); ^{13}C NMR, 13.0, 23.5, 31.8, 34.6, 37.8, 40.1, 48.2, 123.5, 124.1, 125.3, 127.2, 128.4, 131.5, 132.4, 133.8, 137.1, 168.5; HRMS (ES) *m*/*z* 294.1864, calcd for $C_{20}H_{24}NO$ 294.1858.

2.1.3. Compound ***11****.* To a solution of methyltriphenylphosphonium bromide (13 g, 0.037 mol) in dry THF (150 mL) was added *n*-butyllithium (15 mL, 2.5 M in hexane, 0.037 mol) at 0 °C. The mixture was stirred at 0 °C for 1 h and a solution of the known[34] aldehyde **10** (8.0 g, 0.031 mol) in dry THF (30 mL) was added at 0 °C. The mixture was stirred overnight at room temperature, concentrated in vacuo, giving a residue, which was dissolved in ethyl acetate, washed with water, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to afford **11** (7.8 g, 100%). ^1H NMR 1.37 (s, 9H), 1.60–2.20 (m, 8H), 3.27 (m, 1H), 3.48 and 3.60 (m, 1H), 4.88 (m, 4H), 5.70–6.00 (m, 2H); ^{13}C NMR, 20.8, 28.0, 28.6, 36.0, 37.2, 48.6, 66.0, 79.2, 111.0, 114.2, 138.4, 142.2, 154.3; HRMS (ES) *m*/*z* 274.1774, calcd for $C_{15}H_{25}NO_2Na$ 274.1783.

2.1.4. Compound ***12****.* An ethylene gas purged solution of **11** (2.0 g, 8 mmol) in dry methylene chloride (50 mL) containing 10% mol Grubbs II generation catalyst was stirred at reflux for 24 h, cooled, and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to afford **12** (1.8 g, 100%). ^1H NMR 1.39 (s, 9H), 1.78 (m, 5H), 2.10–2.70 (m, 3H), 3.25–3.60 (m, 2H), 5.40–5.90 (m, 2H); ^{13}C NMR, 22.1, 28.0, 30.8, 34.5, 35.3, 38.9, 40.4, 47.3, 73.9, 78.5, 128.9, 136.1, 154.1; HRMS (ES) *m*/*z* 246.1467, calcd for $C_{13}H_{21}NO_2Na$ 246.1470.

2.1.5. Compound ***8*** *from* ***12****.* To a solution of **12** (1.0 g, 4.5 mmol) in dry methylene chloride (50 mL) was added trimethylsiyl iodide (1.8 g, 9.0 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature, quenched by addition of methanol, concentrated in vacuo giving a residue, which was dissolved in dry methylene chloride (50 mL). Triethylamine (2.4 mL, 18 mmol) and *trans*-styrylacetyl chloride (made from *trans*-styrylacetic acid (1.0 g, 6.2 mmol) and thionyl chloride (15 mL) at reflux for 3 h) were added sequentially. The mixture was stirred overnight at room temperature and concentrated to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to provide **8** (0.6 g, 50%).

2.1.6. Conversion of ***8*** *to* ***9****.* An ethylene gas purged solution of **9** (0.2 g, 0.8 mmol) in dry methylene chloride (20 mL) containing 10% mol Grubbs II generation catalyst was stirred at reflux for 24 h,

cooled, and concentrated in vacuo to give a residue, which was subjected to column chromatography (25% acetone/hexane) on silica gel to afford **9** (70 mg, 50%). ^{1}H NMR 1.48 (m, 1H), 1.71 (m, 2H), 1.93 (m, 5H), 2.87 (q, J=18.00 Hz, 2H), 3.32 (m, 1H), 3.92 (m, 1H), 4.94 (q, J=13.00 Hz, 1H), 5.79 (m, 3H); ^{13}C NMR, 19.8, 28.2, 32.7, 36.4, 37.6, 43.1, 66.4, 114.8, 121.9, 129.3,137.7,167.0; HRMS (ES) m/z 192.1390, calcd for $C_{12}H_{18}NO$ 192.1388.

*2.1.7. Compound **14**.* A solution of the known[11] pyrrolidine derivative **13** (2 g, 8 mmol) in HCl/ethyl acetate (3 N, 50 mL) was stirred for 3 h at room temperature, concentrated in vacuo giving a residue that was dissolved in dry methylene chloride (50 mL). A solution of the residue made by sequentially adding triethylamine (2 mL) and *trans*-styrylacetyl chloride (made from *trans*-styrylacetic acid (1.6 g, 10 mmol) and thionyl chloride (20 mL) at reflux for 3 h) was stirred overnight at room temperature and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to provide **14** (1.1 g, 45%). ^{1}H NMR 1.84–2.25 (m, 8H), 3.23 (m, 2H), 3.47 (m, 1H), 3.66 (m, 1H), 4.99 (m, 4H), 5.81 (m, 1H), 6.12 (m, 1H), 6.41 (m, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR, 22.2, 28.7, 35.4, 35.7, 40.6, 49.2, 68.5, 111.9, 114.3, 123.3, 126.2, 127.2, 128.4, 132.6, 136.4, 138.5, 140.5, 142.0, 168.8; HRMS (ES) m/z 318.1827, calcd for $C_{20}H_{25}NONa$ 318.1834.

*2.1.8. Conversion of **14** to **9**.* An ethylene gas purged solution of **14** (1.0 g, 3.4 mmol) in dry methylene chloride (50 mL) containing 10% mol Grubbs II generation catalyst, was stirred at reflux for 24 h, cooled, and concentrated in vacuo to give a residue, which was subjected to column chromatography (25% acetone/hexane) on silica gel to afford **9** (0.52 g, 80%).

*2.1.9. Compound **23**.* To a solution of LEDA (made from diethylamine (16 mL, 0.154 mol) in THF (700 mL) and *n*-butyllithium (60 mL, 0.15 mol, 2.5 M in hexane)) at −78 °C was added a solution of the known[25] oxazolidinone **21** (23 g, 0.126 mol) in dry THF (50 mL). The mixture was stirred at −78 °C for 20 min and then HMPA (26 mL, 0.173 mol) was added. After an additional 30 min, a solution of 5-bromo-1-pentene (23 g, 0.16 mol) in THF (50 mL) was added. The resulting mixture was stirred overnight at room temperature, concentrated in vacuo to afford a residue, which was dissolved in dichloromethane (400 mL), washed with water. The organic layer was dried and concentrated in vacuo to give a residue, which was purified by short path distillation (bp 90–120 °C, 0.2 mmHg) to provide the pentenylated product **22** as a clear oil (15.6 g, 50%). $[\alpha]_D^{23}$ −13.20 (c 2.1, MeOH). ^{1}H NMR 0.87 (s, 9H), 1.40–1.90 (m, 6H), 2.00–2.15 (m, 3H), 2.80–2.90 (m, 1H), 2.90–3.05 (m, 1H), 4.10–4.20 (s, 1H), 4.90–5.00 (m, 2H), 5.70–5.85 (m, 1H); ^{13}C NMR, 23.0, 24.2, 24.7, 33.7, 35.63, 36.3, 57.4, 71.7, 104.9, 114.7, 138.3, 178.5; HRMS (ES) m/z calcd for $C_{15}H_{25}NO_2$ (M+1) 252.1964, found 252.1960.

The pentenylated oxazolidinone **22** (7.6 g, 0.03 mol) was dissolved in 100 mL of MeOH/H_2O (6:1). Silica gel (7.6 g, 200–400 mesh) was added to the solution and the resulting suspension was stirred at room temperature for 48 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo to give a white solid, which was triturated with ethyl ether to give **23** as a white solid (5.3 g, 95%), mp 300 °C (dec). $[\alpha]_D^{23}$ −6.40 (c 1.1, MeOH). ^{1}H NMR (D_2O) 1.30–1.50 (m, 2H), 1.75–1.85 (m, 1H), 1.90–2.20 (m, 7H), 2.30–2.50 (m, 1H), 3.35–3.50 (m, 2H), 5.05–5.20 (m, 2H); 5.80–5.97 (m, 1H); ^{13}C NMR, 15.9, 16.6, 25.6, 27.8, 28.4, 38.7, 67.56, 108.0, 131.3, 169.2; HRMS (ES) m/z calcd for $C_{10}H_{17}NO_2$ (M+1) 184.1338, found 184.1337.

*2.1.10. Compound **27**.* The substituted L-proline **23** (2.0 g, 11 mmol) and Me_4NOH (2.2 g, 0.012 mol) were dissolved in 50 mL of dry acetonitrile. The mixture was stirred at room temperature until a clear solution formed. $(Boc)_2O$ (3.9 g, 0.018 mol) was then added and stirring was continued for 2 d. On the third day, another 0.82 equiv of $(Boc)_2O$ (1.8 g, 0.009 mol) was added, and the mixture was stirred for 2 d. The acetonitrile was removed in vacuo, and the residue was partitioned between ethyl acetate and water. The aqueous layer was acidified with 1 N HCl aqueous solution to pH 2–3 and extracted with ethyl acetate. The extracts were dried and concentrated in vacuo to give the Boc-derivative **24** as white crystals (2.9 g, 94%), mp 92–93 °C. $[\alpha]_D^{23}$ −50.40 (c 30.0, MeOH). ^{1}H NMR 1.20–1.40 (m, 2H), 1.40–1.70 (d, 9H), 1.70–2.00 (m, 4H), 2.00–2.40 (m, 4H), 2.60–2.90 (s, 1H), 3.30–3.90 (m, 2H), 4.90–5.20 (m, 2H), 5.70–6.00 (m, 1H); ^{13}C NMR, 22.7, 23.4, 28.4, 33.5, 33.8, 35.1, 49.3, 70.5, 82.06, 115.1, 138.0, 157.1, 174.9, 180.6; HRMS (ES) m/z calcd for $C_{15}H_{25}NO_4$ (M+Na) 306.1681, found 306.1677.

Following the procedure described by Ono,[35] the proline derivative **24** (6.0 g, 21 mmol) was dissolved in benzene. DBU (4.0 g, 26 mmol) was added followed by a solution of methyl iodide (4.0 mL, 64 mmol) in benzene. A white precipitate appeared after ca. 10 min. The mixture was stirred at reflux overnight and concentrated in vacuo to give a residue, which was washed with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to afford the corresponding ester **25** as a clear liquid (5.4 g, 80%). $[\alpha]_D^{23}$ +13.80 (c 2.2, MeOH); 98% ee (determined by HPLC analysis). ^{1}H NMR 1.30–1.50 (d, 11H), 1.75–2.20 (m, 9H), 3.30–3.45 (m, 1H), 3.70 (s, 3H), 4.90–5.10 (m, 2H), 5.70–5.90 (m, 1H); ^{13}C NMR, 22.8, 28.3, 33.9, 34.6, 37.5, 48.5, 52.0, 67.4, 79.9, 114.9, 138.5, 153.8, 175.6; HRMS (ES) m/z calcd for $C_{16}H_{27}NO_4$ (M+1) 320.1838, found 320.1831.

To a solution of the ester **25** (10 g, 34 mmol) in dry ethyl ether (200 mL) was added a solution of lithium borohydride (35 mL, 70 mmol, 2 M in THF) at 0 °C. The mixture was stirred overnight at room temperature and quenched by the addition of satd sodium bicarbonate. The organic layer was separated, dried, and concentrated in vacuo to afford a residue, which was subjected to column chromatography (50% acetone/hexane) on silica gel to provide the corresponding alcohol **26** (8.2 g, 90%) as an oil. $[\alpha]_D^{23}$ +6.80 (c 0.90, MeOH). ^{1}H NMR 1.40–1.70 (m, 13H), 1.70–2.20 (m, 8H), 3.30–3.40 (m, 2H), 3.63 (s, 2H), 4.90–5.05 (m, 2H), 5.20–5.50 (s, 1H), 5.70–5.90 (m, 1H); ^{13}C NMR, 22.1, 23.8, 28.5, 32.0, 34.1, 48.8, 67.6, 69.4, 80.0, 114.5, 138.8, 156.2; HRMS (ES) m/z calcd for $C_{15}H_{27}NO_3$ (M+Na) 292.1889, found 292.1886.

To a solution of the alcohol **26** (6.0 g, 22 mmol) in dry methylene chloride (100 mL) at 0 °C under nitrogen was added triethylamine (7 mL) and 40 mL of the sulfur trioxide pyridine complex (12 g) in dimethyl sulfoxide. The mixture was stirred overnight at room temperature, quenched by the addition of satd sodium chloride. The organic layer was separated, washed with water, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **27** (6 g, 100%) as an oil. $[\alpha]_D^{23}$ +2.60 (c 0.6, MeOH). ^{1}H NMR 1.20–1.50 (d, 9H), 1.70–2.20 (m, 8H), 3.20–3.70 (m, 2H), 4.90–5.30 (m, 5H), 5.70–5.90 (m, 1H), 9.30–9.50 (d, 1H); ^{13}C NMR, 22.9, 28.2, 32.1, 34.0, 70.9, 80.9, 115.1, 138.2, 153.5, 199.9; HRMS (ES) m/z calcd for $C_{15}H_{25}NO_3$ (M+Na) 290.1732, found 290.1739.

*2.1.11. Compound **28**.* To a solution of $CH_3COCN_2PO(OMe)_2$ (6.0, 31 mmol) in methanol (30 mL) at room temperature under nitrogen was added potassium carbonate (8.0 g, 58 mmol). After stirring for 10 min, a solution of **27** (6.0 g, 22 mmol) in methanol (5 mL) was added to the mixture, which was then stirred overnight at room temperature. Filtration gave a filtrate, which was concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **28** (4.7 g, 80%) as an oil. $[\alpha]_D^{23}$ −9.20 (c 0.8, MeOH). ^{1}H NMR 1.47 (s, 9H), 1.50–1.60 (m, 1H), 1.60–1.90 (m, 2H), 1.90–2.40 (m, 7H), 3.20–3.35 (m, 1H),

3.50–3.80 (m, 1H); 4.80–5.10 (m, 2H), 5.70–5.90 (m, 1H); ^{13}C NMR, 22.5, 28.5, 33.7, 38.6, 40.7, 47.9, 59.5, 69.3, 79.8, 86.8, 114.7, 138.5, 154.2; HRMS (ES) *m*/*z* calcd for $C_{16}H_{25}NO_2$ (M+1) 286.1783, found 286.1792.

*2.1.12. Compound **15**.* To a solution of **28** (6.0 g, 22.8 mmol) in dry dichloromethane (10 mL) at room temperature under nitrogen was added TMSOTf (10.0 g, 45 mmol). After stirring for 30 min, the mixture was concentrated in vacuo to afford a pale yellow residue to which dichloromethane was added. After cooling the solution to 0 °C, dry triethylamine (7 mL) and then acryloyl chloride (5 mL, 62 mmol) were added. The resulting mixture was stirred overnight at room temperature, washed with 1 N HCl followed by water, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **15** as a liquid (2.3 g, 50%). $[\alpha]_D^{23}$ −88.20 (*c* 24.0, MeOH). ^{1}H NMR 1.30–1.40 (m, 1H), 1.60–1.90 (m, 3H), 1.90–2.20 (m, 6H), 2.30–2.40 (m, 1H), 2.40–2.45 (m, 1H), 3.55–3.65 (m, 1H), 3.75–3.95 (m, 1H), 4.90–5.10 (m, 2H), 5.65–5.70 (m, 1H), 5.70–5.90 (m, 1H), 6.30–6.40 (m, 1.6H), 6.90–7.05 (m, 0.4H); ^{13}C NMR, 22.0, 23.6, 24.2, 33.6, 37.0, 39.6, 40.4, 41.7, 48.0, 61.0, 70.2, 72.9, 85.6, 114.7, 126.7, 127.9, 129.5, 138.5, 163.6; HRMS (ES) *m*/*z* calcd for $C_{13}H_{17}NO$ (M+1) 218.1545, found 218.1561.

*2.1.13. Compound **30**.* By following the procedure described by Ono,[35] the known[26] acid **29** (3.0 g, 11 mmol) was dissolved in benzene. DBU (1.7 g, 11 mmol) was added followed by a solution of methyl iodide (2 mL, 32 mmol) in benzene. A white precipitate appeared after ca. 10 min. The mixture was stirred at reflux overnight and concentrated in vacuo to give a residue, which was washed with water and extracted with ethyl acetate. The organic layers were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to afford **30** as a clear liquid (2.5 g, 80%). ^{1}H NMR 1.30–1.50 (d, 9H), 1.70–2.10 (m, 6H), 2.15–2.40 (m, 1H), 3.30–3.45 (m, 1H), 3.69 (s, 3H), 4.80–5.10 (m, 2H), 5.70–5.90 (m, 1H); ^{13}C NMR, 22.7, 28.3, 33.3, 37.4, 48.5, 52.0, 67.3, 79.9, 114.5, 138.2, 153.7, 175.3; HRMS (ES) *m*/*z* calcd for $C_{15}H_{25}NO_4$ (M+Na) 306.1681, found 306.1678.

*2.1.14. Compound **31**.* To a solution of **30** (10 g, 35 mmol) in dry ethyl ether (400 mL) was added a solution of lithium borohydride (35 mL, 70 mmol, 2 M in THF) at 0 °C. The mixture was stirred for 8 h at room temperature and quenched with satd sodium bicarbonate and separated. The organic layer was dried and concentrated in vacuo to afford a residue, which was subjected to column chromatography (50% acetone/hexane) on silica gel to provide **31** (8.1 g, 90%) as an oil. ^{1}H NMR 1.40 (s, 9H), 1.60–2.00 (m, 6H), 2.10–2.20 (m, 1H), 3.25–3.40 (m, 1H), 3.50–3.60 (m, 1H), 4.80–5.00 (m, 2H), 5.20–5.35 (m, 1H), 5.70–5.85 (m, 1H); ^{13}C NMR, 21.9, 28.3, 31.7, 33.9, 48.6, 67.3, 68.9, 79.8, 114.2, 138.4, 155.9; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{26}NO_3$ (M+1) 256.1913, found 256.1901.

*2.1.15. Compound **32**.* To a solution of **31** (6.0, 23 mmol) in dry methylene chloride (100 mL) at 0 °C under nitrogen was added triethylamine (7 mL) and 40 mL of the sulfur trioxide pyridine complex (12 g) in dimethyl sulfoxide. The mixture was stirred overnight at room temperature, quenched with satd sodium chloride, washed with water, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **32** (4.5 g, 75%) as an oil. ^{1}H NMR 1.30–1.50(d, 9H), 1.70–2.20 (m, 8H), 3.40–3.70 (m, 2H), 4.90–5.10 (m, 2H), 5.70–5.85 (m, 1H), 9.30–9.50 (d, 1H); ^{13}C NMR, 22.8, 28.1, 31.9, 33.8, 48.1, 70.6, 80.9, 114.7, 137.8, 153.4, 199.5; HRMS (ES) *m*/*z* calcd for $C_{14}H_{23}NO_3$ (M+Na) 276.1576, found 276.1579.

*2.1.16. Compound **33**.* To a solution of $CH_3COCN_2PO(OEt)_2$ (6.0 g, 31 mmol) in methanol (50 mL) at room temperature under nitrogen was added potassium carbonate (8.0 g, 58 mmol) resulting in a pale yellow solution. After stirring for 10 min, a solution of **32** (6.0 g, 24 mmol) in methanol (5 mL) was added to the mixture, which was then stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **33** (3.8 g, 65%) as an oil. ^{1}H NMR 1.47 (s, 9H), 1.70–2.10 (m, 5H), 2.10–2.40 (m, 3H), 3.20–3.40 (m, 1H), 1.90–2.00 (m, 1H), 2.00–2.10 (m, 1H), 2.70–2.85 (m, 1H), 3.10–3.25 (m, 1H), 3.50–3.80 (m, 1H), 4.80–5.10 (m, 2H), 5.70–5.90 (m, 1H); ^{13}C NMR 22.5, 29.1, 38.3, 40.6, 47.9, 60.0, 69.6, 114.6, 138.0, 154.6; HRMS (ES) *m*/*z* calcd for $C_{15}H_{23}NO_2$ (M+Na) 272.1626, found 272.1618.

*2.1.17. Compound **17**.* To a solution of compound **33** (6.0 g, 24 mmol) in dry dichloromethane (10 mL) at room temperature under nitrogen was added TMSOTf (5.0 g, 22 mmol). After stirring for 30 min, the mixture was concentrated in vacuo to afford a pale yellow residue, to which dichloromethane was added and cooled in ice-water bath. Dry triethylamine, *trans*-styrylacetyl chloride (made from *trans*-styrylacetic acid (1.6 g, 10 mmol) and thionyl chloride (20 mL)) were added. The resulting mixture was stirred overnight at room temperature, washed with 1 N HCl aqueous solution followed by water, dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography (20% acetone/hexane) on silica gel to provide **17** as a liquid (3.5 g, 50%). ^{1}H NMR 1.80–2.20 (m, 5H), 2.20–2.40 (m, 2H), 2.50–2.70 (m, 1H), 3.20–3.25 (m, 2H), 3.40–3.55 (m, 1H), 3.65–3.75 (m, 1H), 4.85–5.15 (m, 2H), 5.70–5.90 (m, 1H), 6.35–6.55 (m, 2H), 7.20–7.55 (m, 5H); ^{13}C NMR, 23.6, 29.4, 36.7, 39.6, 40.4, 48.5, 60.8, 70.5, 85.5, 114.7, 123.0, 126.2, 127.3, 128.5, 132.6, 138.0, 169.0; HRMS (ES) *m*/*z* calcd for $C_{20}H_{23}NO$ (M+1) 294.1858, found 294.1864.

*2.1.18. Conversion of **15** to **16**.* A solution of **15** (0.5 g, 2.3 mmol) in dry methylene chloride (500 mL) containing 10% mol Grubbs II generation catalyst was stirred at reflux for 5 h, cooled, and concentrated in vacuo to give a residue, which was subjected to column chromatography (10% acetone/hexane) on silica gel to afford **16** (0.44 g, 100%) as an oil. $[\alpha]_D^{23}$ −5.60 (*c* 1.1, MeOH). ^{1}H NMR 1.40–1.60 (m, 2H), 1.70–1.90 (m, 4H), 1.90–2.10 (m, 2H), 2.20–2.40 (m, 2H), 3.00–3.20 (m, 1H), 4.30–3.45 (m, 1H), 5.65–5.75 (m, 1H), 5.80–5.90 (m, 1H), 5.55–5.65 (m, 1H); ^{13}C NMR, 17.8, 20.0, 23.8, 30.1, 33.0, 42.0, 63.7, 119.7, 131.7, 135.1, 138.3, 165.6; HRMS (ES) *m*/*z* calcd for $C_{12}H_{15}NO$ (M+1) 190.1232, found 190.1237.

*2.1.19. Conversion of **16** to **38**.* A solution of **16** (0.30 g, 1.6 mmol) and Pd/C (10%, 30 mg) in MeOH (100 mL) under a hydrogen atmosphere was stirred for 5 h. The filtrate obtained by filtration was concentrated in vacuo giving a residue, which was subjected to column chromatography (50% acetone/hexane) on silica gel to afford **38** (0.25 g, 81%) as an oil. $[\alpha]_D^{23}$ −4.60 (*c* 0.58, MeOH). ^{1}H NMR 1.30–2.00 (m, 12H), 2.10–2.20 (m, 1H), 2.30–2.40 (m, 2H), 2.45–2.55 (m, 1H), 3.40–3.50 (m, 1H), 3.75–3.85 (m, 1H); ^{13}C NMR, 19.6, 20.1, 22.7, 23.4, 28.8, 29.9, 30.8, 35.9, 40.1, 43.8, 64.0, 168.7; HRMS (FAB) *m*/*z* calcd for $C_{12}H_{19}NO$ (M+1) 194.1545, found 194.1550.

*2.1.20. Conversion of **38** to **41**.* A solution of Lawesson's reagent (2.1 g, 5.2 mmol) and **38** (0.5 g, 2.6 mmol) in toluene (50 mL) was stirred at reflux for 4 h, cooled, and concentrated in vacuo to give a residue, which was subjected to column chromatography (dichloromethane to 20% acetone/hexane) on silica gel to afford **41** as a white solid (0.42 g, 77%), mp 86–88 °C. $[\alpha]_D^{23}$ −4.20 (*c* 0.65, MeOH). ^{1}H NMR 1.30–1.80 (m, 12H), 1.90–2.20 (m, 3H), 2.45–2.55 (m, 1H), 2.90–3.05 (m, 1H), 3.15–3.25 (m, 1H), 3.75–3.85 (m, 1H), 4.15–4.25 (m, 1H); ^{13}C NMR, 19.4, 22.3, 23.2, 28.8, 29.1, 35.4, 39.3,

40.0, 52.1, 67.7, 195.4; HRMS (ES) *m*/*z* calcd for $C_{12}H_{19}NS$ (M+1) 210.1316, found 210.1316.

*2.1.21. Conversion of **41** to **40**.* To solution of **41** (450 mg, 2.2 mmol) in anhydrous ethyl ether (5 mL) was added methyl triflate (0.36 mL, 3.2 mmol), and the mixture was stirred for 30 min at room temperature. The solution was extracted with Et_2O and 1 N HCl and the resulting aqueous layer was extracted again with CH_2Cl_2 and satd $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtrated, and then concentrated in vacuo to give a residue, which was subjected to column chromatography (CH_2Cl_2/MeOH=20:1) to afford *S*-methyl-thioiminium salt **40** (380 mg, 80%). ^{1}H NMR 1.30–1.56 (m, 4H), 1.65–1.89 (m, 6H), 2.00–2.04 (m, 1H), 2.14–2.25 (m, 3H), 2.45–2.53 (m, 1H), 3.05–3.18 (m, 2H), 3.70 (t, 1H, *J*=10.50 *Hz*), 3.92–3.98 (m, 1H); ^{13}C NMR 15.3, 18.8, 20.0, 20.1, 23.1, 28.1, 29.1, 30.5, 33.5, 36.4, 52.3, 73.2, 187.5; HRMS (ES) *m*/*z* calcd for $C_{13}H_{22}NS^+$ (M) 224.1473, found 224.1472.

*2.1.22. Conversion of **40** to **39**.* To solution of $LiAlH_4$ (1.0 M in THF, 0.76 ml, 0.76 mmol) in anhydrous ethyl ether (10 mL) was added **40** (170 mg, 0.76 mmol), and the mixture was stirred for 3 h at room temperature. The solution was diluted with 1 N HCl and extracted with Et_2O. The resulting aqueous layer was extracted again with CH_2Cl_2 and satd $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated in vacuo to give a clear liquid **39** (106 mg, 78%). ^{1}H NMR 1.25–1.40 (m, 4H), 1.50–1.63 (m, 4H), 1.68–1.88 (m, 9H), 2.83–2.90 (m, 3H), 3.04–3.10 (m, 1H); ^{13}C NMR 20.1, 20.4, 22.0, 24.1, 25.1, 29.4, 29.7, 30.3, 35.2, 36.8, 43.9, 48.9; HRMS (ES) *m*/*z* calcd for $C_{12}H_{22}N$ (M+1) 180.1752, found 180.1750.

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Supplementary data

This material can be found on the online version. Contained in this are ^{1}H and ^{13}C NMR spectra of all previously unidentified compounds, and X-ray crystallographic data. Supplementary data for this article can be found in the online version, at 10.1016/j.tet.2010.06.027.

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