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A Facile and Efficient Synthesis of 3,3-Dimethyl Isopropylidene Proline From (+)-3-Carene

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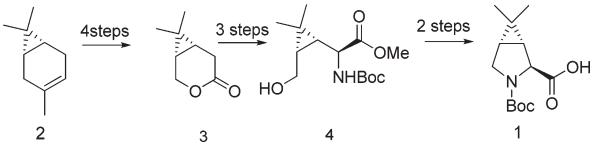

A highly efficient and practical route to 3,4-isopropylidene proline **I**, starting from (+)-3-carene, was developed. The three continuous stereocenters were constructed using the inherent chirality of the starting natural product **2**. The overall yield for the 12-step synthesis is 34%. The optimized sequence leading to **1** has been successfully applied on a multigram scale, thereby establishing the practicality of this route.

An estimated 3% of the world's population is infected with the Hepatitis C virus, and this infection is the leading cause of chronic liver disease.[1] To this day, PEGylated α-interferon alone or in combination with the nucleoside analogue Ribavirin constitutes the most effective therapy. The current line of treatment is effective only in 40% of the patient population and is known to cause adverse side effects. Due to the urgent need for a more tolerable and efficacious regimen, the past decade has seen an emergence of therapies targeting the key enzymes involved in the replication and maturation of the virus.[2]

Hepatitis C virus is a 9.6 Kb positive-stranded RNA virus which encodes a 3000 amino acid polyprotein. The polyprotein is processed by cellular and virally encoded proteases

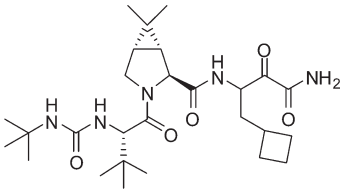

FIGURE 1. Boceprevir (SCH 503034).

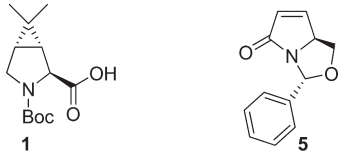

FIGURE 2. Amino acid **1** and lactam **5**.

to structural and nonstructural proteins. The N-terminal side of the nonstructural protein NS3 contains the NS3 protease, a chymotrypsin-like serine protease which catalyzes the cleavage of the NS3−NS4A, one of essential processes during replication of the virus. The importance of this function had made NS3−4A protease inhibitors an attractive target for drug discovery by several groups[3] over the past decade. Our research in the Schering-Plough Research Institute resulted in many potent HCV NS3 protease inhibitors including SCH 503034 (Figure 1), Boceprevir, which is now in clinical trials .

During our lead identification process, an inhibitor containing leucine at P2 was found to possess excellent in vitro activity but unfortunately lacked activity in the cellular assay. On the other hand, leads with proline at P2 had moderate enzyme binding and some cellular activity. Conferring from the above observations and literature precedence, a nonproteogenic amino acid mimicking a constrained leucine moiety, 3,4-dimethylcyclopropyl proline, **1**, was envisioned.

Madalengoitia and co-workers reported the first synthesis of the unusual amino acid of type **I**.[4] Their synthesis involved stereoselective cyclopropanation of pyroglutamic acid derived unsaturated lactam **5** with sulfur ylides (Figure 2).

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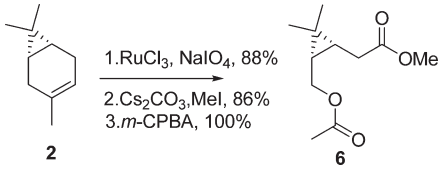
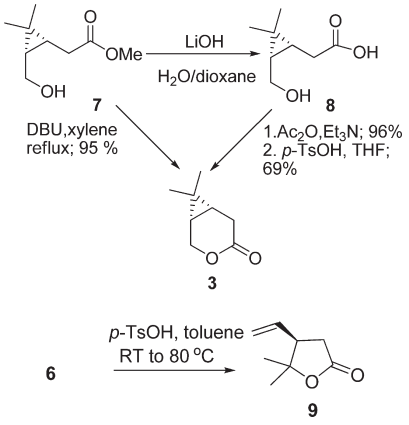
SCHEME 1. Oxidation of Carene



SCHEME 2. Lactonization



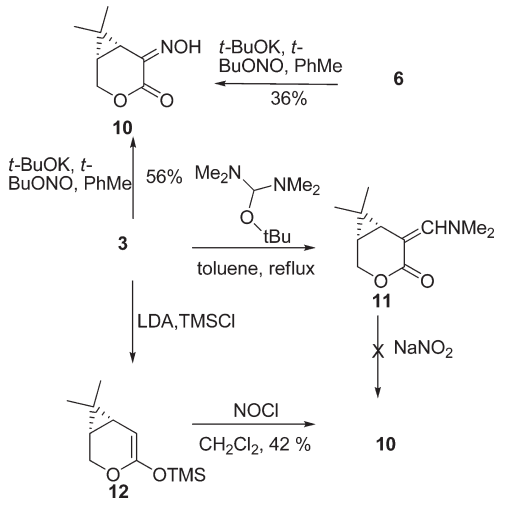
Synthesis of intermediate *O*,*N*-acetal **5** was achieved through a multistep sequence in moderate yield.[5] Moreover, the use of phenyl selynyl bromide to generate the olefin was impractical due to its prohibitive cost and potential toxicity. The need to develop an efficient, scalable route to proline derivative **1** led to the synthetic route described in this report.

The current synthesis started from the commercially available optically pure (+)-3-carene possessing the desired stereochemistry at C(3) and C(4). Ring contraction to the five-carbon skeleton began with Ru-based oxidative cleavage[6] of the olefin **2** to the corresponding ketoacid, which in turn was esterified to obtain the methyl ester in 86% yield. Baeyer−Villiger oxidation of the ketoester afforded acetate **6** in excellent yield (Scheme 1).

Deacetylation of **6** to **7** was achieved with potassium carbonate. Unfortunately, attempts to directly lactonize **7** under basic conditions[7] resulted in hydrolysis to acid **7**. However, it was possible to convert hydroxyl acid **8** to lactone **3** by acetylating the alcohol followed by *p*-TsOH-catalyzed ring closure to give the desired lactone. Alternatively, the hydroxy ester **7** could be readily cyclized to the corresponding lactone under refluxing conditions in the presence of catalytic amounts of DBU (Scheme 2). Attempts to cyclize the acetate **6** or the corresponding hydrolyzed product **8** with *p*-TsOH[8] led to the unexpected opening of the *gem*-substituted cyclopropane ring followed by rearrangement to lactone **9** (Scheme 2).

Introduction of the amine unit on the carbon α to the carbonyl of **3** was achieved through an oximation, reduction sequence. However, this fairly straightforward

SCHEME 3. Oximation



transformation turned out to be the most problematic step in the synthetic route (Scheme 3). Conversion of lactone **3** or acetate **6** to the oxime **10** using either *tert*-butyl or isoamyl nitrite in the presence of potassium *tert*-butoxide[9] gave variable yields (30−56%).

Functionalization of the lactone using Bredereck's reagent[10] to give the corresponding α-dimethylaminomethylene-substituted lactone **11** proceeded smoothly, but treatment of this lactone with sodium nitrite failed to yield the desired oxime. Other exploratory experiments to convert **3** to **10** by trapping the enolate of the lactone, **12**, with either sodium nitrite or nitroso tetrafluoroborate were unsuccessful. However, promising results were observed when nitrosyl chloride[11] was used as the electrophile, thus oxime **10** could be obtained in 42% yield along with quantitative amounts of leftover starting material (lactone), presumably due to the instability of the enolate (Scheme 3).

In an effort to optimize the yield of the oximation, we then attempted trapping the enolate of the lactone with ethyl formate.[12] The reaction proceeded quantitatively but gave a mixture of the desired compound **13** along with **14**, the product formed by nucleophilic attack of the lactone by the ethoxide and trapping of the corresponding alcohol with ethyl formate (Scheme 4).

Fortunately, treatment of this mixture with sodium nitrite in the presence of acetic acid led to oximation of both compounds **13** and **14** to yield a mixture of **10** and **15** in 85% yield over the two steps (Scheme 4). The oximated lactone could be easily reduced to the Boc-protected amine **16** with desired stereoselectivity most likely controlled by the inherent disposition of the dimethyl cyclopropane unit. On the other hand, when the oximated acyclic ester **15** was treated under the same conditions, the Boc-protected amine **15** was formed exclusively. Variations of

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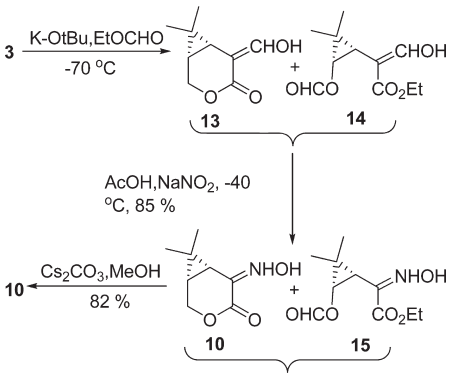
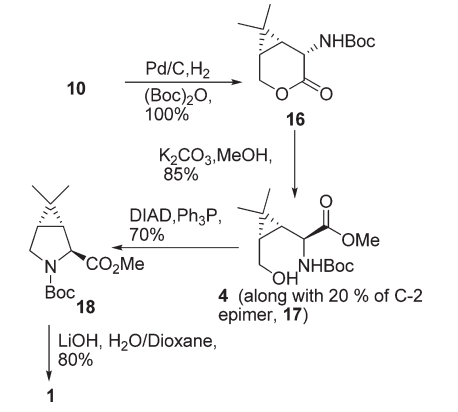
SCHEME 4. Alternate Route for Oximation



SCHEME 5. Ring Contraction via Mitsunobu



either the catalyst or solvent did not affect the outcome of this reaction.

Fortuitously, when the crude reaction from the oximation reaction was treated with Cs_2CO_3 in MeOH, oxime **15** spontaneously cyclized to give **10**. Methanolysis of the lactone **16** gave hydroxy *N*-Boc esters **4** and **17** as a mixture of epimers at C-2 (4:1). Attempts to cyclize **4** via the corresponding mesylate or the imidazoyl ester activated by methyl iodide led mainly to lactone **9** (Scheme 2). Subjecting the epimeric mixture of **4** and **17** under Mitsunobu conditions gave the desired substituted proline **18**. Finally, when the epimeric ester **18** was hydrolyzed using LiOH, the desired thermodynamically favored 3,4-isopropylidene proline **1** was formed exclusively in 80% yield (Scheme 5).

In summary, a highly efficient route to 3,4-isopropylidene proline was developed starting from an inexpensive starting material and common laboratory reagents. The inherent chirality of (+)-3-carene is elegantly utilized to make the process highly efficient and to introduce the third stereocenter in the title compound **1**. The 12-step sequence leading to the peptidomimetic core **1**, with an overall yield of 32%, has been optimized and successfully applied on a multigram scale (100 g), establishing the practicality of this route.

Experimental Section

(1*S*,6*R*)-7,7-Dimethyl-3-oxabicyclo[4.1.0]heptan-4-one (3): A solution of **7** (70 g, 406 mmol) in 1.1 L of xylenes was refluxed with DBU (30.9 g, 203 mmol) for 18 h, and methanol was removed from the distillate. The solution was cooled, washed with cold 1 N HCl and then with brine, and dried over anhyd Na_2SO_4. Then, it was filtered and evaporated off the solvent, and the crude product was purified via silica gel column chromatography with EtOAc−CH_2Cl_2 to afford **3** (54 g, 95%) as a colorless oil which solidifies to an amorphous white solid: IR (thin film, cm^{-1}) 2948, 1727,1458,1377,1253, 1171, 1139, 1072, 976; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.71 (dd, J = 7.14 Hz, 1H), 4.04 (dd, J = 6.59 Hz, 1H), 2.75 (dd, J = 7.14 Hz, 1H), 2.16 (dd, J = 5.49 Hz, 1H), 1.16 (s, 3H), 1.27−1.18 (m, 2H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 176.6, 62.9, 30.6, 28.9, 24.6, 23.2, 18.9, 15.3; EIMS calcd for $C_8H_{12}O_2$ $[M + H]^+$ 141.1797, found 141.0909; $[\alpha]^{25}_D$ −89.07 (*c* 0.5732, CH_2Cl_2).

(1*S*,5*E*,6*R*)-7,7-Dimethyl-3-oxabicyclo[4.1.0]heptane-4,5-dione-5-oxime (10): A solution of **3** (42gm, 300 mmol) in 300 mL of anhydrous toluene was treated with 90% *t*-BuONO (102 mL, 720 mmol). To this mixture was added KO*t*BU (45 g, 400 mmol) in six portions over 20 min at 35 °C. Then 180 mL of anhydrous methanol was added, the temperature rose to 40 °C, and stirring continued at 40 °C for 2.5 h. The mixture was cooled, quenched with a cold solution of 1.1 L of 10% aqueous sodium dihydrogen phosphate and 20 mL of 12 N HCl, then extracted with EtOAc. The extracts were washed with 5% aqueous $NaHCO_3$ and then brine, dried over anhyd Na_2SO_4, filtered, and evaporated in vacuo. The residue (25 g) was chromatographed on 150 g of silica gel using a gradient of 35:65 EtOAc−CH_2Cl_2 to obtain 29 g (56%) of **10** as an amorphous solid: IR (thin film, cm^{-1}) 2948, 1687, 1611, 1452, 1427, 1330, 1310, 1195, 1139, 1003; ^1H NMR ($CDCl_3$, 500) δ 4.82 (dd, J = 5.99 Hz, 1H), 4.55 (dd, J = 12.61 Hz, 1H), 2.40 (d, J = 8.82 Hz, 1H), 1.52−1.49 (m, 1H), 1.27 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 161.4, 145.3, 66.9, 27.7, 23.2, 22.9, 16.3 ppm; HRMS(FAB) calcd for $C_8H_{11}NO_3$ $[M + H]^+$ 170.18, found 170.30; (ESI) calcd for $C_8H_{11}NO_3$ $[M + Na + AcN]^+$ 233.0902, found 233.0852; $[\alpha]^{25.5}_D$ +184.29 (*c* 1.1075, CH_2Cl_2). Anal. Calcd: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.47; H, 6.96; N, 8.19.

Methyl (2*S*)-[(*tert*-Butoxycarbonyl)amino][(1*R*,3*S*)-3-(hydroxymethyl)-2,2-dimethylcyclopropyl]acetate (4): A solution of **16** (35 g, 137 mmol) in 350 mL of anhyd methanol was treated with K_2CO_3 (12 g, 86 mmol) at room temperature for 2 h. Volatiles were evaporated off, and then the mixture was quenched with 0.6 L of 10% aq KH_2PO_4. It was extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhyd Na_2SO_4, filtered, and evaporated off to get 33 g of **4** (8:2 mixture of α-*S*/α-*R*). This was not separated to proceed to the next step. For analytical purposes, a portion was chromatographed with Et_2O−hexane (60:40) to obtain a pure α-*S*-epimer of the title compound: IR (thin film, cm^{-1}) 3358, 2954, 1741, 1690, 1511, 1366, 1158, 1016; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.2 (br s, 1H), 4.05 (br s, 1H), 3.81 (m, 1H), 3.76 (s, 3H), 3.65 (m, 1H), 1.43 (s, 9H), 1.14 (s, 3H), 1.05 (s, 3H), 1.05 (m, 1H), 0.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 155.8, 81.0, 59.7, 52.8, 30.9, 29.6, 29.2, 28.7, 19.9, 16.1 ppm; HRMS calcd for $C_{14}H_{25}NO_5$ $[M + Na]^+$ 310.1630, found 310.1621; $[\alpha]^{25}_D$ −62.9 (*c* 1, MeOH). Anal. Calcd: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.48; H, 8.75; N, 5.10.

Further elution provided the α-*R*-epimer (**17**): IR (thin film, cm^{-1}) 3353, 2954, 1691, 1514, 1365, 1158, 1016; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.95 (br s, 1H), 4.03 (m, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 3.71 (m, 1H), 1.44 (s, 9H), 1.13 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 0.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 155.7, 80.7, 60.1, 53.3, 50.3, 30.4, 29.2, 19.6, 16.1, 15.3 ppm; HRMS calcd for $C_{14}H_{25}NO_5$ $[M + H]^+$ 288.1811, found 288.1776; $[\alpha]^{25}_D$ −32.8 (*c* 1, MeOH). Anal. Calcd: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.46; H, 8.69; N, 4.74.

3-*tert*-Butyl 2-methyl (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo-[3.1.0]hexane-2,3-dicarboxylate (18): A solution of Ph_3P (21.6 g, 82.4 mmol) in 250 mL of anhydrous THF was cooled to −10 °C and treated with DIPA (16.2 g, 80.2 mmol) in drops.

After 5 min, the mixture was treated with a solution of **4** (mixture of *R* and *S*, 19.7 g, 68.5 mmol) in 35 mL of THF and stirred for 10 min, and then heated at reflux for 3 h, cooled, and evaporated off in vacuo. The residue was diluted with 450 mL of methanol−water (1:1) and then extracted with hexane (7 × 200 mL). The combined extracts were washed with 20 mL of methanol−water (1:1) and brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated in vacuo. The residue was taken up in 400 mL of hexane, suction-filtered through a pad of 30 g silica gel, and the silica pad was eluted with an additional 210 mL of EtOAc−hexane (1:9). The combined filtrates were evaporated in vacuo to leave **18** (14.5 g, 78%) as a mixture of two epimers (analytical data provided in Supporting Information).

(1*R*,2*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-6,6-dimethyl-3-azabicyclo-[3.1.0]hexane-2-carboxylic acid (1): A solution of **18** (14.5 g, 53.8 mmol) in 1,4-dioxane (270 mL) was treated with 135 mL of 1 M aqueous LiOH, and the mixture was heated at 80 °C for 4 h. The mixture was cooled, concentrated in vacuo to half volume, diluted with 200 mL of water, and extracted with hexane. The aqueous layer was chilled and treated with a solution of 9 mL of 12 N HCl in 50 mL of 10% aqueous KH_2PO_4, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to afford **1** (11.9 g, 86%), rotameric mixture because of Boc: IR (thin film, cm^{-1}) 2976, 1744, 1699, 1390, 1367, 1170, 1128; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.77 (br s, 1H, COOH), 4.20 (d, J = 30.75 Hz, 1H), 3.62 (m, 1H), 3.44 (m, 1H), 1.55 (m, 1H), 1.43 and 1.39 (s, 9H), 1.25 (m, 1H), 1.03 (s, 3H), 0.97and 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.3, 178.1, 154.9, 153.7, 80.9, 80.5, 60.1, 46.8, 46.5, 32.2, 30.9, 28.6, 27.4, 27.7, 19.3, 12.8 ppm; HRMS calcd for $C_{13}H_{21}NO_4$ $[M + H]^+$ 256.1548, found 256.1547; $[\alpha]^{25}_D$ +23.77 (*c* 0.5636, CH_2Cl_2). Anal. Calcd: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.95; H, 8.18; N, 5.65.

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