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Synthesis of 1-substituted 2,3-dihydro-7*H*-oxepin-4-one from an amino acid

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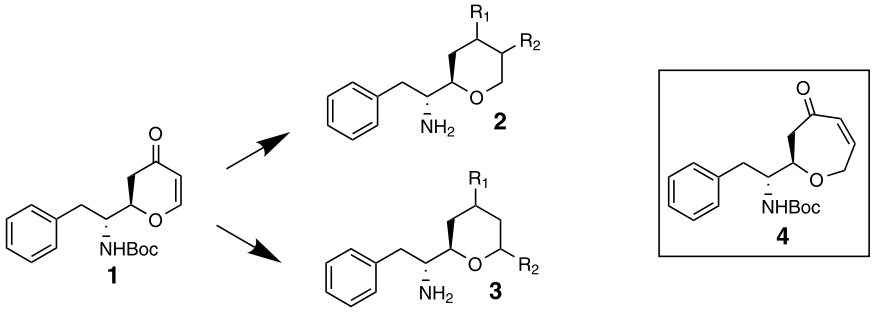
Abstract—3,4-Dihydro-7*H*-oxepin-4-one system is potentially convenient starting material for the synthesis of diverse oxepane-based compounds such as peptidomimetics. We have developed a simple, five-step synthesis of 1-substituted-3,4-dihydro-7*H*-oxepin-4-one **11** from Boc-D-phenylalanine using a combination of statine synthesis methodology and olefin ring closing metathesis reaction.

Recently, we described our efforts to apply the tetrahydropyrane scaffold in peptidomimetic research. We made a series of 2,4,5- **2**[1] and 2,4,6-trisubstituted **3**[2] tetrahydropyrans that show biological activity with melanocortin receptors. Subsequently, we realized that a conceivable extension of this design might include an oxepane system (Scheme 1) since the seven-membered ring structure could expand conformational space sampled by oxacyclic peptidomimetics thus allowing for fine-tuning their spatial properties. Following successful transformations of 3,4-dihydro-2*H*-pyran-4-one **1** to the desired peptidomimetics **2** and **3**, we decided to explore synthetic opportunities for making the 2,3-dihydro-7*H*-oxepin-4-one **4** that could serve as a starting point for the future syntheses of oxepane-based analogs including peptidomimetics. Although synthesis of the oxepane ring was given substantial attention during the past 20 years,[3–5] we were unable to find literature precedence for making the corresponding 2,3-dihydro-7*H*-oxepin-4-one **4** and, consequently, we designed a method for its preparation.

Our preparation method of the title compound **4** involves transformations of 4-substituted 4-amino-3-hydroxybutanoic acids, also known as statines, concluding with an olefin metathesis reaction to form a seven-membered oxepin ring. The methodology is shown in Scheme 2. Statines are convenient starting materials because their syntheses are well known[4–11] and some of them are also commercially available.

One traditional method of statine synthesis comprises a reaction of Cbz- or Boc-protected amino acid with 1,1′-carbonyldiimidazole followed by treatment with an enolate ion formed from alkyl acetate. We used this chemistry employing the enolate ion of Weinreb acetamide and Boc-D-PheOH **5** under conditions described for the reaction of ethyl acetate with Boc amino acids.[12]



Scheme 1.

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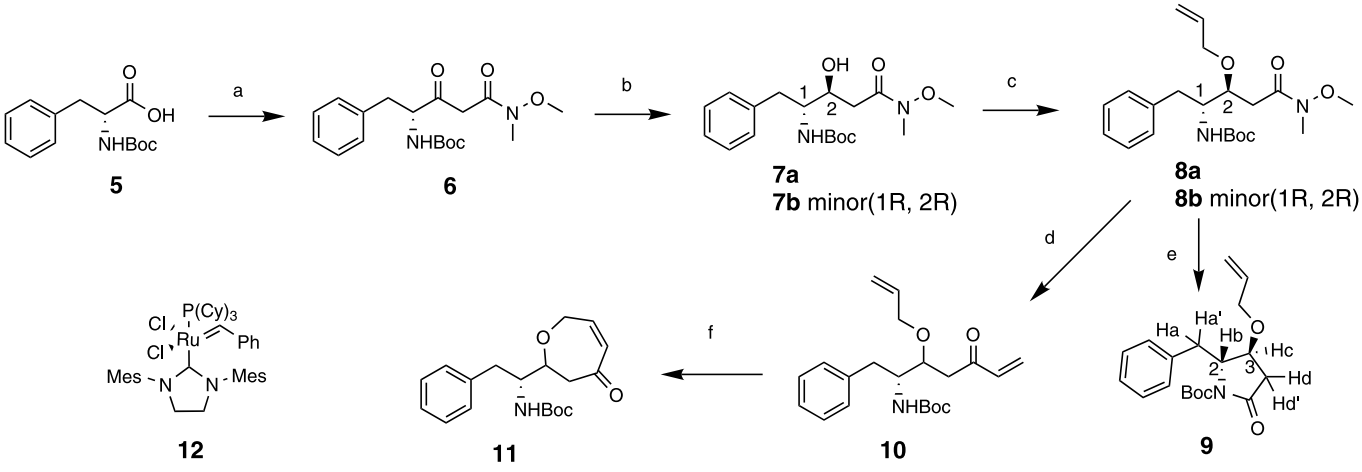
The resulting ketoamide **6**[†] was subjected to diastereoselective (4:1) reduction of the ketone group to produce a mixture of diastereoisomeric alcohols **7a** and **7b**[‡] that were readily separated on a silica column. We initially assigned 1*R*,2*S* configuration to the major isomer **7a** following the rationale provided by Harris and Joullie[12] for similar reductions of ketoacids with potassium borohydride. Later in this paper, we present further support for this assignment using spectral analysis and modeling of lactam **9**.

The first alkene moiety, required for the metathesis reaction, was introduced by allylation of the hydroxyl group in **7a** and **7b**. For this purpose, we used a palladium-mediated reaction under neutral conditions[13] thus avoiding basic environment and circumventing possible base-related side-reactions such as retroaldol or elimination of the 1-carbonyl-3-hydroxy system. The diastereoisomers **8a** and **8b**[§] were readily separated on a silica column. In order to convert the latter materials to 1,3-enone, we envisioned a reaction of the Weinreb



Scheme 2. *Reagents and conditions*: (a) LDA, 1,1′-carbonyldiimidazole, THF, −78°C; (b) KBH_4, MeOH, −4°C; (c) $Pd_3(dba)_2$, bdpb, allylmethylcarbonate, THF; (d) vinylmagnesium bromide, toluene; (e) Grubbs catalyst, DCM, 0.02 M.

[†] Analytical HPLC was performed using a ThermoQuest system equipped with MetaChem, Polaris, C18, 3 μ column 4.6×250 mm column, using linear gradient elution starting from CH_3CN/0.1% phosphoric acid in water (20:80) to 100% CH_3CN over 20 min (1 ml/min). Preparative HPLC was done on Rainin Dynamax and Varian ProStar systems equipped with MetaChem, Polaris, C18 10 μ column 50×250 mm using gradient elution starting from CH_3CN/0.1% trifluoroacetic acid in water to 100% CH_3CN over 50 min. **[1*R*-Benzyl-3-(methoxymethylcarbamoyl)-2-oxopropyl]carbamic acid *tert*-butyl ester 6**. A solution of Boc-D-Phe (6 g, 0.023 mol) in THF (60 ml) was treated with 1,1′-carbonyldiimidazole (4.05 g, 0.025 mol) and stirred at room temp for about 15 min and cooled to −78°C. At the same time, in a separate vessel, *N*-methoxy-*N*-methylacetamide (8.6 ml, 0.081 mol) was dissolved in THF (60 ml) and 2 M LDA (40 ml, 0.08 mol) was added dropwise at −78°C. This anion solution was canulated into the amino acid solution at −78°C. The reaction mixture was stirred for 30 min, quenched with NH_4Cl, warmed to rt, mixed with ether and then treated with water until all solids dissolved. The organic layer was separated, washed with aqueous 5% HCl, saturated. $NaHCO_3$, dried with anhydrous magnesium sulfate and concentrated. Purification a silica column (hexane:EtOAc, 1:1) afforded 4 g (50%) of the product **6**. HPLC t_R 14.07 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.14 (m, 5H), 5.46–5.24 (m, 1H), 4.60–4.32 (m, 1H), 3.60 (m, 3H), 3.7 (s, 2H), 3.17 (s, 3H), 3.15–1.10 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 203.2, 168.1, 155.6, 137.7, 129.7, 128.9, 126.9, 87.0, 80.3, 61.6, 60.9, 55.5, 45.5, 39.5, 37.0, 32.3, 28.5. HRFAB (positive) *m*/*e* 373.1739 calcd for $C_{18}H_{26}N_2NaO_5$ (M+Na)$^+$, found 373.1753.

[‡] **[1*R*-Benzyl-2-hydroxy-3-(methoxymethylcarbamoyl)propyl]carbamic acid *tert*-butyl ester 7a**, 1*R*,2*S* and **7b**, 1*R*,2*R*. The ketone **6** (4 g, 0.0114 mol) was dissolved in MeOH (60 ml), cooled to −40°C and treated with KBH_4 (0.72 g, 0.0133 mol). The reaction mixture was stirred for 1 h at −40°C and quenched with NH_4Cl. The product was extracted with ethyl acetate, dried over $MgSO_4$. The solvents were removed under reduced pressure. The crude product was purified on a silica column (EtOAc:hexane, 6:4) to afford 3.5 g (87%) of alcohols **7a** and **7b**. Compound **7a**: 2.8 g, white solid, mp 90–92°C; α=-38.8° (*c* 2.07, $CHCl_3$); HPLC t_R 12.25 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.17 (m, 5H), 4.75 (d, J=8.4 Hz, 1H), 4.34–4.07 (m, 1H), 4.06–3.86 (m, 2H), 3.65 (s, 3H), 3.18 (m, 3H), 3.12–2.98 (m, 1H), 2.97–2.81 (m, 1H), 2.80–2.48 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.9, 155.9, 138.3, 129.9, 128.6, 126.5, 79.5, 70.3, 61.5, 55.3, 36.1, 35.5, 32.1, 28.5. Compound **7b**: 0.7 g, white solid, mp 115–117°C; α=+57.2° (*c* 2.0, $CHCl_3$); HPLC t_R 12.61 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.16 (m, 5H), 5.13 (d, J=9.9 Hz, 1H), 4.37–4.09 (m, 1H), 4.08–3.92 (m, 1H), 3.85–3.70 (m, 1H), 3.64 (s, 3H), 3.16 (s, 3H), 2.94 (d, J=4.5 Hz, 2H), 2.59 (d, J=6.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.4, 156.2, 138.6, 129.7, 128.7, 126.5, 79.5, 67.2, 61.5, 55.9, 39.0, 35.7, 32.1, 28.6. HRFAB (positive) *m*/*e* 375.1896 calcd for $C_{18}H_{28}N_2NaO_5$ (M+Na)$^+$, found 375.1903.

[§] **[2-Allyloxy-1*R*-benzyl-3-(methoxymethylcarbamoyl)propyl]carbamic acid *tert*-butyl ester 8a**, 1*R*,2*S* and **8b**, 1*R*,2*R*. Tris(dibenzylideneacetone)dipalladium(0) (0.081 g, 0.088 mmol) and 1,4-bis(diphenylphosphino)butane (0.149 g, 0.072 mmol) were suspended in dry THF (1.5 ml) under argon. A solution of **7a** and **7b** diastereoisomeric mixture (1.23 g, 3.5 mmol) and allyl ethyl carbonate (1.2 ml, 10.5 mmol) in dry THF (10 ml) was added, and the mixture was refluxed under argon for 12 h. The solvent was removed under reduced pressure and the crude product was purified on a silica column (7:3, hexane:EtOAc) to give 1.1 g (80%) of **8a** and **8b**. Compound **8a**: 0.9 g, α=+12.5° (*c* 2.5, $CHCl_3$); HPLC t_R 15.67 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.13 (m, 5H), 6.2–5.84 (m, 1H), 5.36–5.13 (m, 2H), 4.68 (bs, 1H), 4.20–3.90 (m, 4H), 3.70 (s, 3H), 3.22 (m, 3H), 3.16–2.44 (m, 4H), 1.33 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.0, 155.8, 138.3, 134.9, 129.6, 128.6, 126.6, 117.2, 79.6, 77.8, 71.8, 61.6, 55.2, 37.3, 34.7, 32.5, 28.5. Compound **8b**: 0.2 g, α=+32.9° (*c* 1.4, $CHCl_3$); HPLC t_R 16.38 min; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.15 (m, 5H), 6.45–5.84 (m, 1H), 5.40–5.13 (m, 2H), 4.89 (d, J=9.6 Hz, 1H), 4.16 (dd, J_1=5.4 Hz, J_2=12.6 Hz, 2H), 3.68 (s, 3H), 3.19 (m, 3H), 2.95–2.85 (m, 2H), 2.84–2.54 (m, 2H), 1.4 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.0, 156.0, 138.4, 135.0, 129.5, 128.6, 126.6, 117.1, 79.4, 76.2, 72.0, 61.4, 55.1, 39.3, 34.5, 28.6, 28.2. HRFAB (positive) *m*/*e* 415.2209 calcd for $C_{21}H_{32}N_2NaO_5$ (M+Na)$^+$, found 415.2222.

amide functionality with vinylmagnesium bromide. Recently, this reaction was reported as a means to introduce a vinylketone system that was subsequently utilized for the ring closing metathesis reaction to form carbocyclic six-membered[14] and heterocyclic eight-membered[15] rings containing α,β-unsaturated ketone. In contrast to our expectations, addition of the Grignard reagent to a diastereoisomeric mixture of **8a** and **8b** using 2 equiv. of vinylmagnesium bromide produced, after quenching, the lactam **9**¶ as the major product with only small amount (below 10%) of the desired enone. This result was not surprising, however, given a propensity of linear γ-amino acids for the formation of five-membered lactam ring. A diastereisomeric mixture of the desired enones **10a** and **10b**‖ was obtained in 51% yield when we increased the excess of Grignard reagent to 5 equiv.

Because lactam **9** was obtained in good yield, we presumed that it came from the major isomer **8a** and that created an opportunity to confirm independently the configuration of **8a**. After analyzing COSY and ^{1}H NMR spectra of lactam **9**, we established 1*R*,2*S* configuration to **8a**. A support for this assignment provides a lack of coupling between protons Hb (3.79 ppm) and Hc (4.36 ppm). In addition, the proton Hb appears to be coupled only to protons Ha and Ha′. These data imply that Ha and Hb may form a dihedral angle close to 90°. In fact, a molecular model of 2*R*,3*S* lactam **9** with geometry optimized at ab initio 3-21G level shows 93° angle between these two protons. If the configuration was 2*R*,3*R*, the same calculations produced 37° angle and we would expect a more complicated spectral pattern for the protons Hb and Hc. Assignment of 2*R*,3*S* stereochemistry to **9** supports 1*R*,2*S* configuration of **8a** as the major isomer.

Formation of the oxepanone ring was accomplished by means of metathesis reaction as intended. The ring-closing methatesis (RCM) has been used extensively for making the oxepin ring.[16–25] A more recent variant of this reaction allowed for RCM of double bonds in α,β-unsaturated carbonyl systems[17,21] using a new ruthenium catalyst based on 1,3-dimethyl-4,5-dihydroimidazol-2-ylidene ligand. We obtained 2,3-dihydro-7*H*-oxepin-4-one **11**** in excellent yields with a commercial catalyst **12** based on this ligand. While writing this paper we have found a recent communication describing a synthesis of oxepan-3-one using RCM reaction of conjugated ketones with the same catalyst.[26]

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¶ **3*S*-Allyloxy-2*R*-benzyl-5-oxopyrrolidine-1-carboxylic acid *tert*-butyl ester 9**. When only 2 equiv. of vinylmagnesium chloride were used in the reaction of **8a** and **8b**, the lactam **9** was formed in 1 h and was isolated using an identical procedure to one employed for **10a** with 60% yield of **9** as viscous oil. $\alpha = -27.6°$ (*c* 1, $CHCl_3$); HPLC t_R 16.61 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.15 (m, 5H), 5.73–5.65 (m, 1H), 5.09–5.04 (m, 1H), 5.00–4.95 (m, 1H), 4.36 (dd, $J_1 = 3.4$ Hz, $J_2 = 10.0$ Hz, 1H), 3.79 (d, $J = 5.3$ Hz, 1H), 3.78–3.76 (m, 1H), 3.65–3.59 (m, 1H), 3.2 (dd, $J_1 = 3.4$ Hz, $J_2 = 13.4$ Hz, 1H), 2.63 (dd, $J = 10$ Hz, $J_2 = 13.7$ Hz, 1H), 2.58–2.43 (m, 2H), 1.6 (s, 9H). HRFAB (positive) *m*/*e* 332.1861 calcd for $C_{19}H_{25}NO_4$ $(M+H)^+$, found 332.1866.

‖ **(2-Allyloxy-1*R*-benzyl-4-oxohex-5-enyl)carbamic acid *tert*-butyl ester 10**. A diastereoisomeric mixure of **8a** and **8b** (0.125 g, 0.32 mmol) was dissolved in toluene (3 ml), the solution was cooled to −10°C and treated with 1 M vinyl magnesium chloride (1.6 ml, 1.6 mmol). The reaction mixture was stirred for 3 h at −10°C, quenched with 10% ammonium chloride and extracted with ethyl ether. Then solvent was removed in vacuo and the crude product was purified on a silica column (8:2, hexane:EtOAc) to give 0.06 g (51%) of **10**. HPLC t_R 17.19 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.18 (m, 5H), 6.44–6.34 (m, 1H), 6.28–6.20 (m, 1H), 6.00–5.84 (m, 2H), 5.34–5.25 (m, 1H), 5.24–5.16 (m, 1H), 4.52–4.40 (m, 1H), 4.14–3.92 (m, 3H), 3.12–3.00 (m, 1H), 2.98–2.68 (m, 3H), 1.33 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 199.1, 155.6, 138.2, 137.1, 134.9, 128.6, 128.6, 126.6, 117.3, 79.6, 77.5, 71.8, 55.1, 42.3, 37.3, 28.5. HRFAB (positive) *m*/*e* 382.1994 calcd for $C_{21}H_{29}NNaO_4$ $(M+Na)^+$, found 382.1980.

** **[1*R*-(4-Oxo-2,3,4,7-tetrahydrooxepin-2-yl)-2-phenylethyl]carbamic acid *tert*-butyl ester 11**. A solution of **10** (0.03 g, 0.084 mmol) in DCM (15 ml) was degassed with argon and RCM catalyst **12** (0.04, 0.0042 mmol) was added. The reaction mixture was stirred for 30 min at 4°C. The solvent was evaporated and the crude product was subjected to silica gel chromatography (1:1, hexanes:EtOAc). The purification afforded product **11** (0.03 g) with 95% yield. Compound **11**: white solid, mp 145–147°C; $\alpha = -74.3°$ (*c* 1, $CHCl_3$); HPLC t_R 14.96 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.16 (m, 5H), 6.38 (dt, $J_1 = 3$ Hz, $J_2 = 12.6$ Hz, 1H), 6.05 (d, $J = 12.9$, 1H), 4.74–4.56 (m, 2H), 4.50–4.38 (m, 1H), 4.08–3.96 (m, 1H), 3.92–3.80 (m, 1H), 3.05 (dd, $J_1 = 4.2$ Hz, $J_2 = 14.1$ Hz, 1H), 3.00–2.86 (m, 2H), 2.85–2.71 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 200.6, 155.5, 144.1, 138.1, 130.5, 129.5, 128.7, 126.7, 79.8, 71.9, 53.7, 48.3, 35.6, 31.8, 28.5. HRFAB (positive) *m*/*e* 354.1681 calcd for $C_{19}H_{25}NNaO_4$ $(M+Na)^+$, found 354.1690.

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