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4,5-Disubstituted *cis*-pyrrolidinones as inhibitors of 17β-hydroxysteroid dehydrogenase II. Part 1: Synthetic approach

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Abstract—17β-Hydroxysteroid dehydrogenase II (17β-HSD II) antagonists may provide an important way into preventing the onset of osteoporosis. The discovery of 4,5-disubstituted *cis*-pyrrolidinones as 17β-HSD II inhibitors led to the development of an efficient intramolecular Michael addition, followed by catalytic hydrogenation to obtain the desired *cis* configuration.

A screening effort identified a novel inhibitor of 17β-hydroxysteroid dehydrogenase II **1** for the treatment of osteoporosis.[1] The screening hit **1** is a close analog of the natural product clausenamide **2**, an active ingredient in the *Clausena lansium* leaves used to treat viral hepatitis (Fig. 1).[2]

The original synthetic approach developed by Hartwig and Born[2] involved a Michael addition followed by a cyclization with sodium methoxide to obtain pyrrolidinone **5** (Scheme 1). Alkylation of the amide and selective hydrolysis/decarboxylation of one of the ester groups yielded a 2:1 ratio of the (±)-*cis* pyrrolidinone **7** and (±)-*trans* isomer **8**. Recrystallization of the two diastereomers afforded the desired (±)-*cis* pyrrolidinone. The aldehyde **9** was obtained via a two step reduction/oxidation process without epimerization at the C-5 position. Alkylation of the *cis* aldehyde **9** afforded only one diastereomer. Chiral chromatography was employed to obtain the desired (*R*,*R*,*R*)-alcohol **1**.

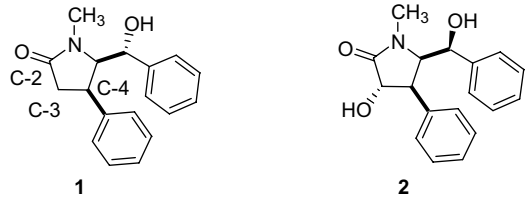

Figure 1. 17β HSD II inhibitor and clausenamide.

Although the original synthetic approach required eight steps and resulted in a 20% overall yield, the low diastereoselectivity (2:1) during the decarboxylation step and the difficulties installing substituents at the C-4 position greatly affected our analoging efforts. Therefore, a more versatile route was examined, which would allow C-4 substitution.

A synthetic approach to obtain the *cis*-pyrrolidinone was envisioned from an intramolecular Michael addition of a substituted alkyne (Scheme 2). Literature precedent confirmed the feasibility of an intramolecular 5-*endo*-*dig* Michael addition to an epoxide or alkyne to obtain the pyrrolinone moiety **10**.[3]

The alkyne **11** was synthesized via an EDCI coupling of the appropriate carboxylic acid[4] **12** with sarcosine ethyl ester **13**. Attempts to produce the pyrrolinone **10** via an intramolecular Michael addition with lithium bis(trimethylsilyl)amide gave low and inconsistent yields. The side products observed were from the addition of molecular oxygen to the ester enolate resulting in an intermediate that decomposed upon work-up to the alkynyl amide **14**. The hydroxy compound **15** was also observed from the oxygen addition to the ester enolate of the pyrrolinone. Purging the reaction with argon prior to treatment with base resulted in improved and

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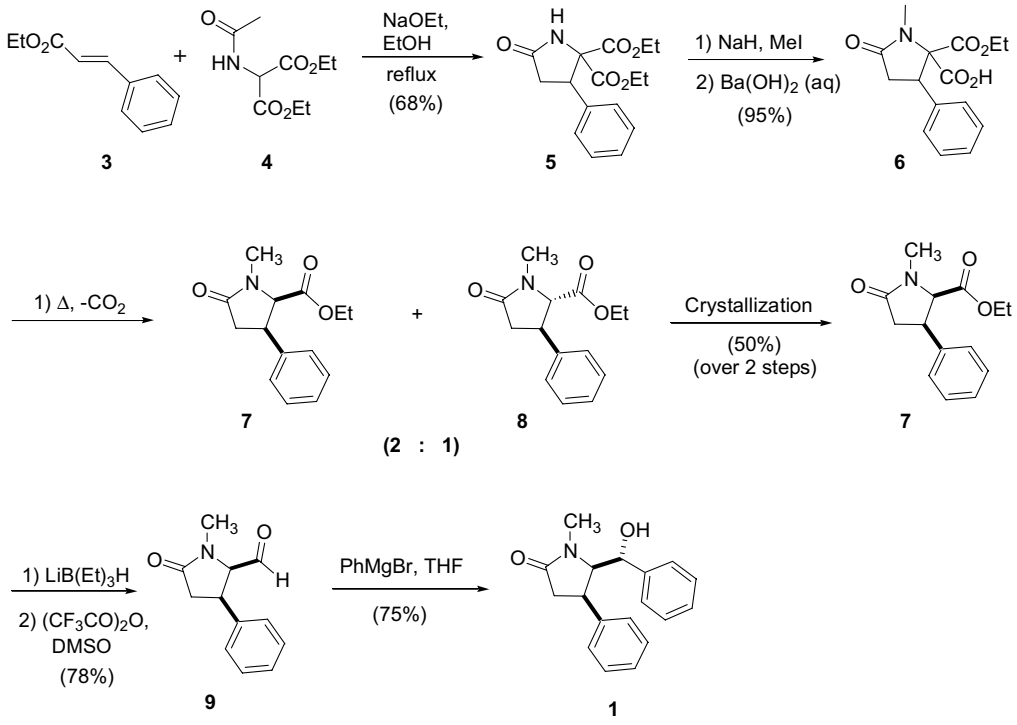
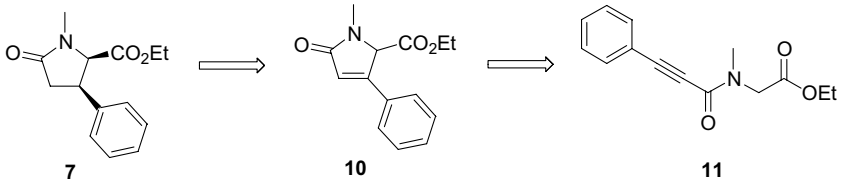


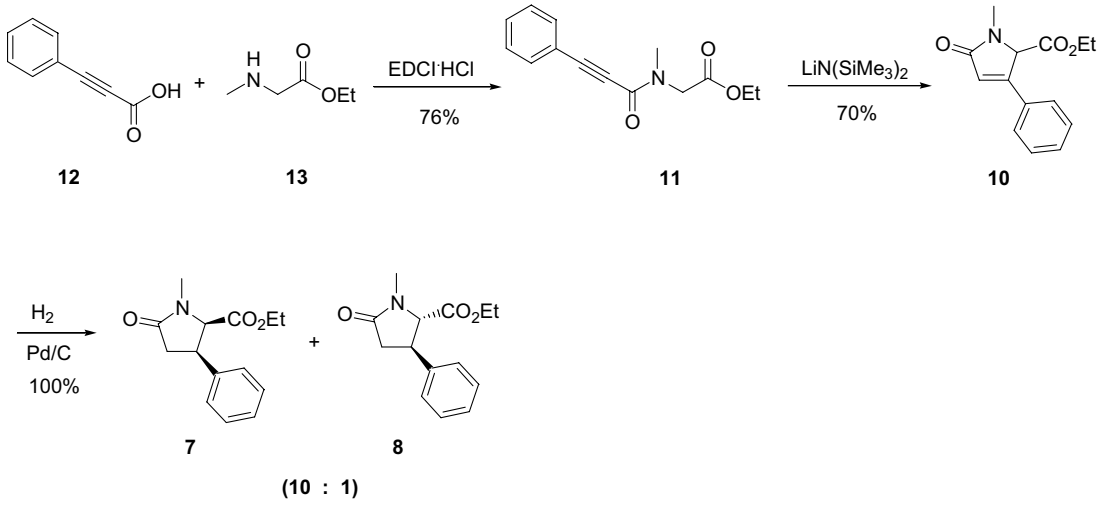
Scheme 1. Synthesis of **2** via Hartwig et al.[2] approach.



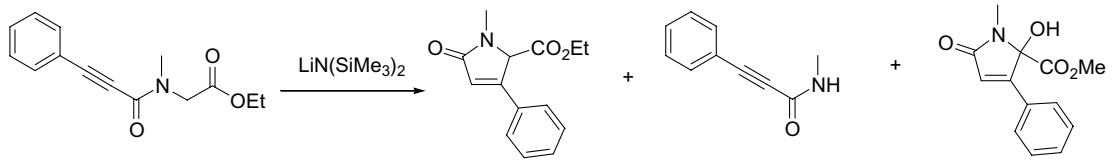
Scheme 2. Retrosynthetic analysis.

reproducible yields of the pyrrolinone **10** with no trace of side products (Schemes 3 and 4).

Hydrogenation of the pyrrolinone **10** using catalytic palladium on carbon produced the desired product in a



Scheme 3. *cis*-Pyrrolidinone via intramolecular Michael addition.



11 10 14 15

Scheme 4. Side products from the Michael addition.

Table 1. Yields of Michael addition product (pyrrolinone) and hydrogenation product (pyrrolidinone)

R	Pyrrolinone yield	Pyrrolidinone yield (*cis*:*trans* ratio)[a]
Methyl	72	5 (14:1)[b]
Propyl	90	37 (*cis* only)[b]
Phenyl	70	100 (10:1)
2-Fluorophenyl	50	100 (12:1)
2-Methoxyphenyl	73	95 (*cis* only)
3-Fluorophenyl	35	97 (12:1)
3-Methoxyphenyl	81	92 (14:1)

[a] Ratios determined by HPLC and Hartwig et al. experimental data.
[b] Yields not optimized.

10:1 ratio of *cis* **7** to *trans* **8** isomers.[5] Here the ratio was not dependent on the C-4 substituent (Table 1). Previous researchers have shown similar results reducing pyrrolinone derivatives to afford predominantly the *cis* isomer.[6]

As shown by Hartwig and Born,[2] the ester **7** could be carried to the secondary alcohol **1** by reduction with lithium borohydride to afford the primary alcohol. Swern oxidation yielded the aldehyde **9**, followed by direct alkylation with the appropriate lithio or Grignard reagent generated the secondary alcohol **1** in high diastereoselectivity. It is noteworthy that the oxidation–addition steps proved to be difficult (0–30%). In this sequence, the aldehyde **9** generated from the Swern oxidation was difficult to handle and was used without purification. However, the use of Dess–Martin reagent generated a cleaner aldehyde for the addition reaction.

In conclusion, the synthetic approach using an intramolecular Michael addition has two distinct advantages over the previous approach: an improved diastereoselectivity for *cis* over *trans* isomers and a shorter three step route with an overall yield of 53%.[7] Additionally, this approach led to the opportunity to vary the C-4 position of the pyrrolidinone core. Further publications of the pharmacological results will be reported in due course.

Acknowledgements

The authors thank Jon Brice for Chiral HPLC work. Synthesis of racemic (4*R*,5*R*)-5-((1*R*)hydroxyphenylmethyl)-1-methyl-4-phenylpyrrolidin-2-one **1** according to the published procedure was performed by Todd Gane and David Gunn. Mass spectra were obtained by Mr. Anthony Paiva and Mr. Stuart Coleman. Assignment of fluorine couplings of ^{13}C NMR spectra were accomplished by Mr. László Musza.

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4. Carboxylic acids were obtained from either a commercial source or synthetically prepared via a Castro–Stevens/Sonogashira coupling, followed by hydrolysis.
5. Ratios determined by comparison to Hartwig and Born experimental data of the *cis* (**7**) and *trans* (**13**) isomers.
6. Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217; Herdeis, C. et al. *Tetrahedron: Asymmetry* **1994**, *5*, 351.
7. Representative experimental procedure: *Ethyl 2-(N-methyl-3-phenylprop-2-ynoylamino)acetate* (**11**): To a 0 °C solution of phenylpropiolic acid (25 g, 0.17 mol), sarcosine ethyl ester hydrochloride (27 g, 0.17 mol, 1 equiv), 4-dimethylaminopyridine (21 g, 0.17 mol, 1 equiv), and 4-methylmorpholine (19 mL, 0.17 mol, 1 equiv) in CH_2Cl_2 (250 mL) was added EDCI·HCl (33 g, 0.17 mol, 1 equiv) in small portions. The resulting mixture was allowed to warm to room temperature and stirrred overnight. The reaction mixture was diluted with CH_2Cl_2, then washed with water, a 0.5 M HCl solution, and a saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography to give ethyl 2-(*N*-methyl-3-phenylprop-2-ynoylamino)acetate (**11**, 32 g, 76%) as an orange oil: TLC (25% EtOAc/hex) R_f 0.32; ^1H NMR ($CDCl_3$ rotomeric mixture) δ 1.28 (t, $J = 7.2$ Hz, 3H), 3.07 (s, 1.2H), 3.35 (s, 1.8H), 4.18–4.26 (m, 3H), 4.38 (s, 1H); 7.35–7.40 (m, 3H), 7.49–7.57 (m, 2H).
5-Ethoxycarbonyl-1-methyl-4-phenyl-3-pyrrolin-2-one (**10**): Argon was bubbled in a solution of ethyl 2-(*N*-methyl-3-phenylprop-2-ynoylamino)acetate (**11**, 20 g, 82 mmol) in THF (100 mL) for 5 min. The solution was cooled to 0 °C treated with a solution of $LiN(SiMe_3)_2$ (1 M in THF, 82 mL, 82 mmol). The resulting mixture was stirrred for

2 h, then was slowly treated with water (20 mL), and diluted with CH_2Cl_2 (200 mL). The organic layer was washed with water (150 mL), a 1 N HCl solution (150 mL), and water (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient from 0% to 50% EtOAc/hex) to give racemic 5-ethoxycarbonyl-1-methyl-4-phenyl-3-pyrrolin-2-one (**10**, 14 g, 70%) as a brown oil: TLC (40% EtOAc/hex) R_f 0.13; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.4 Hz, 3H), 3.03 (s, 3H), 4.12 (m, 2H), 5.13 (s, 1H), 6.46 (s, 1H), 7.39–7.41 (m, 3H), 7.53–7.60 (m, 2H); HPLC ES-MS *m*/*z* (rel abundance) 246 (MH^+, 100%).

(±)-(*4R**,*5S**)-*5-Ethyl-1-methyl-4-phenylpyrrolidin-2-one* (**8**) and (±)-(*4R**,*5R**)-*5-ethyl-1-methyl-4-phenylpyrrolidin-2-one* (**7**): A mixture of 5-ethoxycarbonyl-1-methyl-4-phenyl-3-pyrrolin-2-one (**10**, 1 g, 4 mmol) and 10% palladium on carbon (0.1 g) in EtOH (30 mL) was stirred under a H_2 atmosphere (1 atm) for 1 h. The reaction mixture was filtered through a pad of Celite® with the aid of CH_2Cl_2. The filtrate was concentrated under reduced pressure to yield greater than a 10:1 mixture of (±)-(4R^*,5R^*)-5-ethyl-1-methyl-4-phenylpyrrolidin-2-one (**7**) and (±)-(4R^*,5S^*)-5-ethyl-1-methyl-4-phenylpyrrolidin-2-one (**8**) (1 g, 100%). Ratio of stereoisomers was determined by HPLC and literature Ref. 2. Experimental data only shown for (**7**): TLC (40% EtOAc/hex) R_f 0.13; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 2.64–2.72 (dd, J = 8.8, 16.5 Hz, 1H), 2.88–3.0 (m, 4H), 3.65–4.0 (m, 4H), 4.34–4.36 (d, J = 8.9 Hz, 1H), 7.2–7.35 (m, 5H); HPLC ES-MS *m*/*z* (rel abundance) 248 (MH^+, 100%).