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SYNTHESIS OF 3-OXOAZACYCLOHEPT-4-ENES BY RING-CLOSING METATHESIS. APPLICATION TO THE SYNTHESIS OF AN INHIBITOR OF CATHEPSIN K

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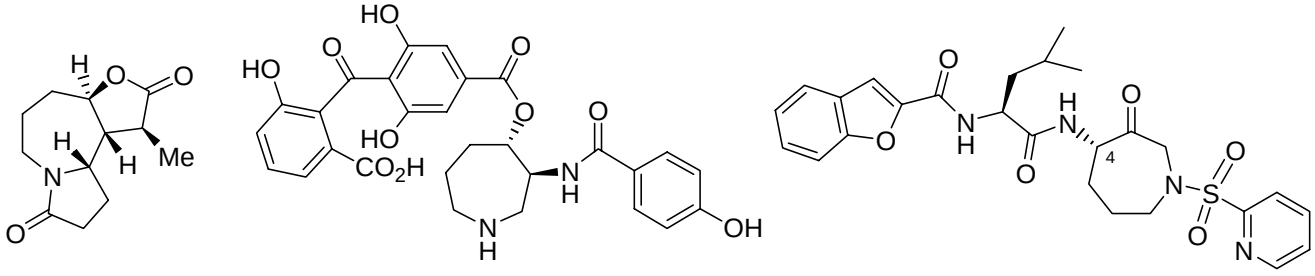
Abstract – The ring-closing metathesis allows the formation of 3-oxoazacyclohept-4-enes from but-3-enamine. By using this methodology, the synthesis of an inhibitor of cathepsin K was achieved in 10 steps from but-3-enamine.

INTRODUCTION†

Seven-membered ring amino compounds are present in a great variety of natural and non-natural products which possess interesting biological properties. These molecules have stimulated the development of an array of methods for their synthesis.[1] We were particularly interested in the synthesis of 3-oxoazacyclohept-4-enes, as these compounds can be the precursors of the cyclic skeleton of biologically active compounds such as stemoamide,[2] an insecticide, balanol,[3] an inhibitor of protein kinase C (PKC) and, more particularly, azepanone (**I**)[4] which is an inhibitor of the cysteine protease cathepsin K (Figure 1).

Figure 1. Representative biologically active compounds with an azacycloheptane skeleton.

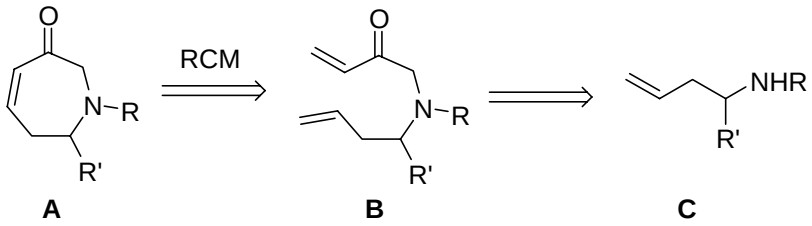


Stemoamide Balanol **I**

† This paper is dedicated to Pr. B. M. Trost on the occasion of his 65th birthday.

The aim of this study was to identify a general and convenient strategy for the synthesis of functionalized 3-oxoazacyclohept-4-enes of type (**A**). The access to compounds of type (**A**) was envisaged by using a ring-closing metathesis (RCM) applied to 1-(3'-alkenylamino)but-3-en-2-ones of type (**B**) which should be obtained from homoallylamines of type (**C**) (Scheme 1).

Scheme 1. Retrosynthetic analysis of azepinones of type (**A**).



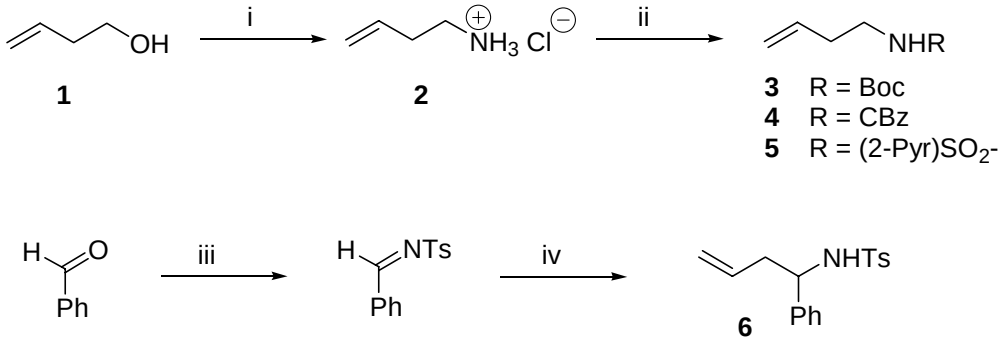
RESULTS AND DISCUSSION

As the ruthenium catalysts, implied in the metathesis reaction, can be poisoned by the presence of non-protected amino groups, compounds (**3**-**6**), in which the amino group was protected with an electron-withdrawing group, were prepared (Scheme 2).[5] The synthesis of compounds (**3**-**5**) (when R' = H and R = Boc, CBz, 2-PyrSO_2-) has been accomplished from but-3-en-1-ol (**1**). The transformation of but-3-en-1-ol (**1**) to the corresponding but-3-enamine (**2**) was achieved by using a Mitsunobu reaction involving phthalimide. Treatment of **1** with phthalimide (1.1 equiv.) in the presence of DIAD (1.1 equiv.) and PPh_3 (1.1 equiv.) in THF at 0 °C for 3 h and hydrazinolysis of the resulting phthalimido compound (H_2N-NH_2, H_2O, EtOH, 80 °C) followed by an acidic work-up led to the chlorohydrate of the but-3-enamine (**2**) with an overall yield of 96%.[6] In order to obtain the protected homoallylamines (**3**, **4** and **5**), the ammonium salt (**2**) was treated, under basic conditions, with respectively di-*tert*-butyl dicarbonate (Et_3N, CH_2Cl_2, rt; **3** = 66% yield), benzoyl chloride (Na_2CO_3, CH_2Cl_2, rt; **4** = 71% yield) and 2-pyridinesulfonyl chloride[7] (Et_3N, CH_2Cl_2, rt; **5** = 88% yield). The *p*-toluenesulfonyl protected homoallylamine (**6**) (R' = Ph, R = Ts) was prepared from benzaldehyde in two steps. The first step was the transformation of benzaldehyde to tosyl imine[8] ($TsNH_2$, TsNa, HCO_2H, H_2O, rt) followed by the addition of allylmagnesium chloride to the tosyl imine (THF, -15 °C) which led to **6** with an overall yield of 56%.

The transformation of but-3-enamines (**3**-**6**) to the desired but-3-enaminoenones (**11**-**14**) was achieved in two steps *via* the stabilized phosphoranes (**7**-**10**). These latter compounds were prepared by alkylation of the amine with triphenylchloroacetonylphosphorane[9] under basic conditions (BuLi, THF, rt) in yields superior to 55%. The obtained phosphoranes (**7**-**10**) were then converted to the α-amino enone (**11**, **12** and **13**) by condensation with acetaldehyde in yields superior to 85%, and to the α-amino enones (**14)** by condensation with formaldehyde in 62% yield (Table 1). The use of acetaldehyde instead of formaldehyde

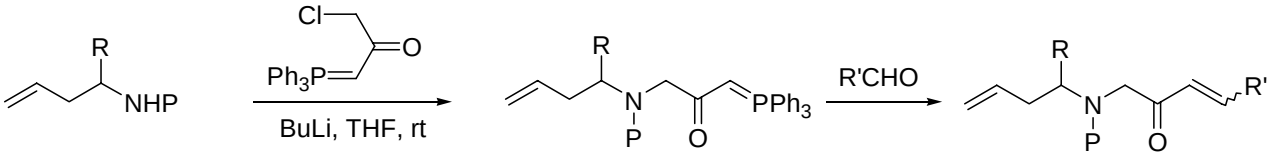
led to substituted terminal alkenes which are less inclined to polymerize during their isolation and purification.

Scheme 2. Synthesis of the homoallylamines (**3**-**6**).



Conditions and reagents: (i) 1°- Phthalimide, DIAD, PPh_3, THF, 0 °C, 2°- hydrazine, H_2O, EtOH, Δ, then 35% aq HCl, rt, 96% (two steps); (ii) Compound (**3**): Boc_2O, Et_3N, CH_2Cl_2, rt, 66%; compound (**4**): CbzCl, Na_2CO_3, CH_2Cl_2, rt, 71%; compound (**5**): (2-Pyr)SO_2Cl, Et_3N, CH_2Cl_2, rt, 88%; (iii) $TsNH_2$, TsNa, HCO_2H/H_2O, rt, 60%; (iv) AllylMgCl, THF, -15 °C, 94%.

Table 1. Synthesis of the ω-unsaturated α-amino enones (**11**-**14**).

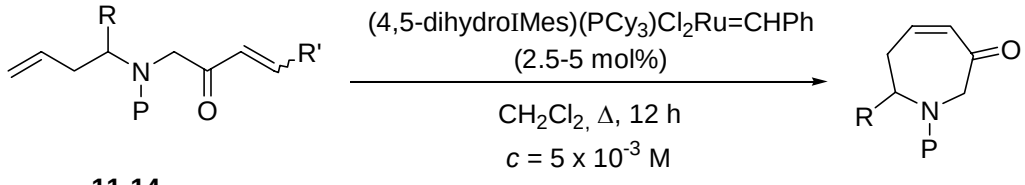


3-**6** **7**-**10** **11**-**14**

3	P = Boc, R = H, R' = Me	**7**	74%	**11**	87%
4	P = CBz, R = H, R' = Me	**8**	90%	**12**	85%
5	P = (2-Pyr)SO_2-, R = H, R' = Me	**9**	94%	**13**	94%
6	P = Ts, R = Ph, R' = H	**10**	57%	**14**	62%

The obtained ω-unsaturated α-amino enones (**11**-**14**) were involved in a RCM reaction and the results are reported in Table 2. All the reactions were carried out with 2.5 to 5 mol% of the second generation Grubbs catalyst [(4,5-dihydroIMes)(PCy_3)Cl_2Ru=CHPh][10] at a concentration of 5×10^{-3} M in refluxing CH_2Cl_2 for 12 h. The seven-membered azacyclic compounds (**15**-**18**) were obtained in yield superior to 90% (Table 2). As this methodology was efficient in obtaining 3-oxoazacyclohept-4-enes from homoallylic amines, its application to the synthesis of a potent azepanone-based inhibitor of the osteoclast-specific cysteine protease cathepsin K, compound (**I**), was achieved (Scheme 1).

Table 2. Synthesis of azepinones (**15-18**).

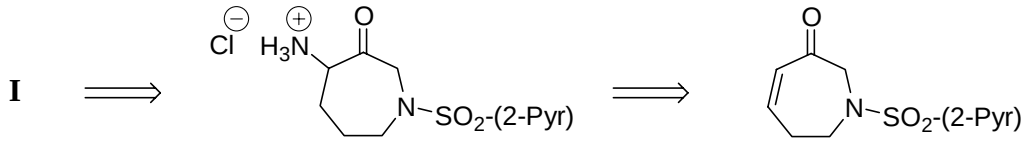


11-14 **15-18**

11	P = Boc, R = H, R' = Me	**15**	90%
12	P = Cbz, R = H, R' = Me	**16**	97%
13	P = (2-Pyr)SO_2-, R = H, R' = Me	**17**	96%
14	P = Ts, R = Ph, R' = H	**18**	99%

Two syntheses of **I** have been disclosed, one non-stereocontrolled synthesis[4] leading to **I** as a mixture of the two epimers at C-4 which were separated by HPLC and one enantioselective synthesis.[11] The shortest synthesis was the non-stereocontrolled synthesis which was achieved in 12 steps from allylamine.[4] To perform the enantiomerically enriched synthesis,[11] an Evans aldol reaction was used as the key-step and 15 steps were necessary to complete the synthesis from aminoacetaldehyde dimethyl acetal. By using our methodology, the synthesis of compound (**I**) as a mixture of the two C-4 epimers was realized in 10 steps from homoallylamine chlorohydrate. In order to introduce the peptido side-chain, the synthesis of compound (**I**) was planed from the α-amino ketone (**20)** which should be obtained from the previously synthesized 3-oxoazacyclohept-4-en-one (**17)** (Scheme 3).

Scheme 3. Retrosynthetic analysis of cathepsin inhibitor (**I**).

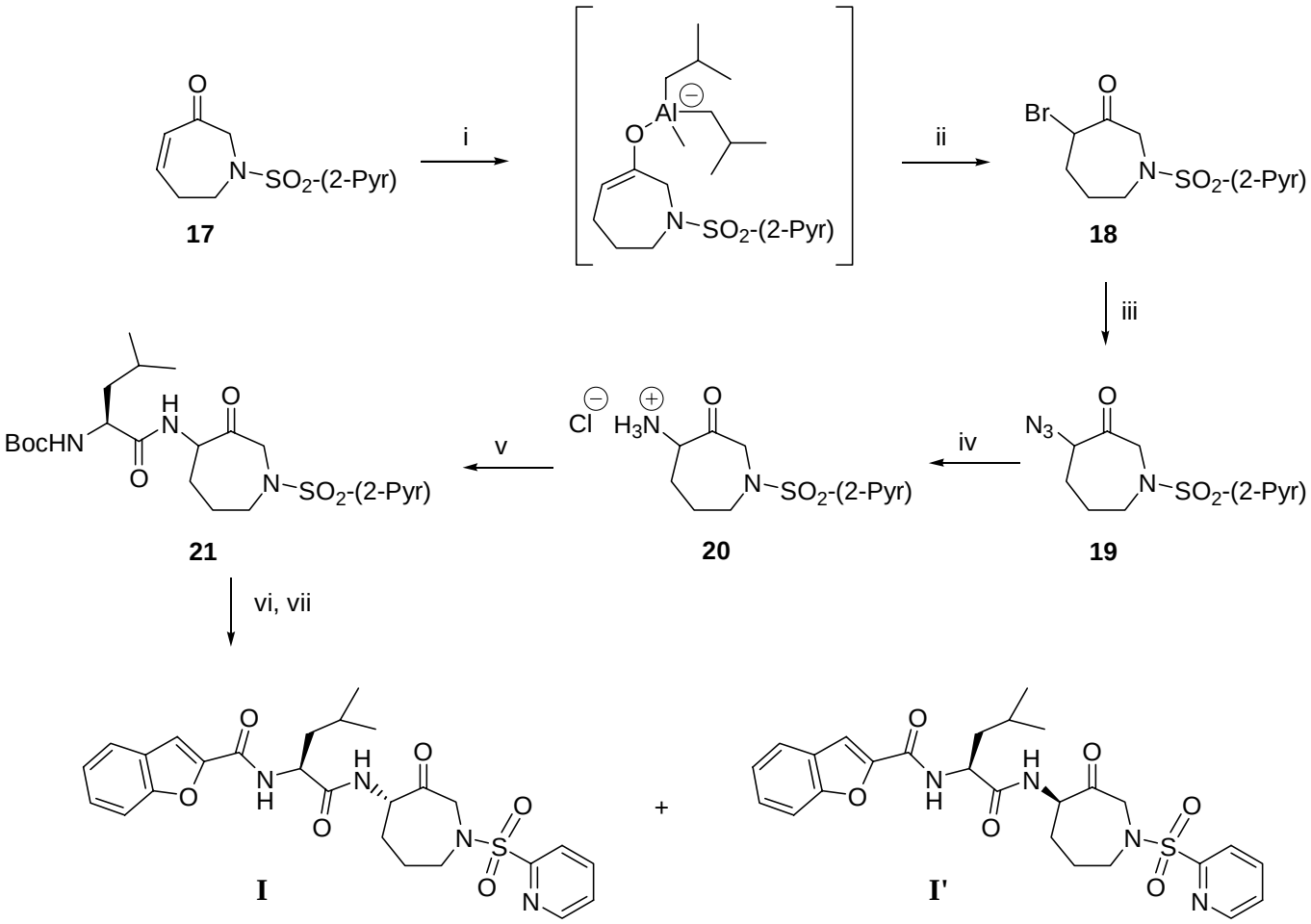


20 **17**

Compound (**17**) was transformed to the azido compound (**19**) in two steps. The first step was the formation of the α-bromoazepanone (**18**) *via* the 1,4-addition of an "hydride" generated by the addition of DIBALH (4 equiv.) in the presence of a cyanocuprate [CuCN (2 equiv.), BuLi (2 equiv.), THF, -50 °C, 2 h] and activation of the resulting intermediate enolate with MeLi (1 equiv.), in the presence of HMPA (3 equiv.), (-50 °C, 30 min) to form a more reactive aluminate enolate which can react with bromine (10 equiv., -50 °C to -20 °C, 1 h) to furnish the α-bromo ketone (**18**).[12,13] Without purification, α-bromo ketone (**18**) was

converted to the α-azido ketone (**19**) in 45% overall yield (from **17**) by treatment with NaN_3 (NaN_3, DMF, rt). After hydrogenation of **19** in acidic conditions (H_2, 10% Pd/C, MeOH/HCl), the resulting chlorohydrate (**20**) was condensed with the *N*-Boc-L-leucine[14] (EDCI, HOBT, Et_3N, CH_2Cl_2, rt) to furnish the desired keto amide (**21**) in a 51% overall yield (from **19**). After cleavage of the *N*-Boc group (4M HCl in dioxane, MeOH) and condensation with benzofuran-2-carboxylic acid in the presence of EDCI and HOBt, compound (**I**)[15] and its epimer (**I'**) were isolated in 52% overall yield (Scheme 4).

Scheme 4. Synthesis of **I**.



Conditions and reagents: (i) 1°- DIBALH (4 equiv.), CuCN (2 equiv.), BuLi (2 equiv.), THF - 50 °C, 2 h, then 2°- HMPA (3 equiv.), MeLi (1 equiv.), -50 °C, 30 min; (ii) Br_2 (10 equiv.), -50°C to -20 °C, 1 h; (iii) NaN_3, DMF (45% from **17**); (iv) H_2, 10% Pd/C, MeOH/HCl; (v) *N*-Boc-L-Leucine, EDCI, HOBt, Et_3N, CH_2Cl_2, rt, 51% (two steps); (vi) 4M HCl in dioxane, MeOH, rt, 2.5 h; (vii) benzofuran-2-carboxylic acid, EDCI, HOBt, Et_3N, CH_2Cl_2, rt, 52% (two steps).

CONCLUSION

By applying a RCM to ω-unsaturated α-amino enones, 3-oxo azacyclohept-4-enes were obtained in good yields. Furthermore, by using this methodology, we were able to shorten the synthesis of compound (**I**), an inhibitor of cathepsin K.

ACKNOWLEDGEMENTS

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