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Novel macrocyclic templates by ring enlargement of ansa-steroids

Stefan Bäurle, Thorsten Blume, Emmanuel Leroy, Anne Mengel,* Christian Parchmann, Kathrin Schmidt and Werner Skuballa

Schering AG, Medicinal Chemistry, Research Center Europe, 13342 Berlin, Germany

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Dedicated to Professor Dr. Johann Mulzer on the occasion of his 60th birthday

Abstract—Ring enlargement of ansa-steroids leads to a variety of novel templates which are suitable for the preparation of diverse libraries of natural product derivatives. Key steps for the synthesis of these highly functionalized templates were either an ozonolysis-derivatization-ring closing metathesis-sequence or a macrolactonization.

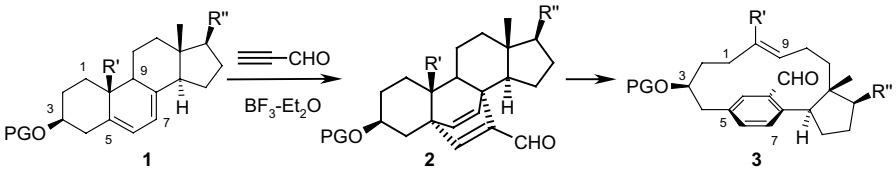
Compound libraries comprising natural compound derivatives are generally regarded as a rich source for hits in the drug discovery process.[1] We recently reported that several compounds of a library originating from the macrocyclic steroid-derived template **3** exhibit remarkable inhibitory activity against phosphatase Cdc25B.[2] Furthermore, we published the synthesis of a 17-membered macrocycle by opening the cyclopentane ring of **3** applying a Wagner–Meerwein rearrangement and ozonolysis.[3] Encouraged by these results we then focused on the transformation of the ansa-steroid **3** to more flexible structures with regard to ring size and functionalization. Due to the enhanced flexibility within the macrocycle, the compounds should show a higher adaptability towards the molecular target resulting in a possible hit enrichment in HTS.

Herein, the synthesis of these second-generation templates starting from steroids is described applying olefin metathesis as well as macrolactonization as key reactions.

Ansa-steroids **3** can be easily obtained by the Winterfeldt–Diels/Alder-retro-Diels/Alder-sequence (Scheme 1).[4]

Ring closing metathesis is known to be a powerful tool for the preparation of macrocycles.[5] The synthesis of **5**, with two terminal alkene functionalities suitable for metathesis, was accomplished starting from **4**. First, the aldehyde **4** was reduced and the hydroxyl groups were protected as silylethers. The disubstituted double bond of **4** was cleaved by ozone at −78 °C and after reductive workup with $NaBH_4$, treatment of the resulting diol with allylbromide under phase transfer conditions afforded bisalkene **5** (Scheme 2).

Cyclization of **5** in the presence of first generation Grubbs catalyst[6] in CH_2Cl_2 led to the 20-membered



Scheme 1. Synthesis of ansa-steroids, R′ = H or Me.

Keywords: Steroids; Macrocycles; Ring closing metathesis; Macrolactonization; Template.
* Corresponding author. Tel.: +49 30 46815529; fax: +49 30 46895529; e-mail: anne.mengel@schering.de

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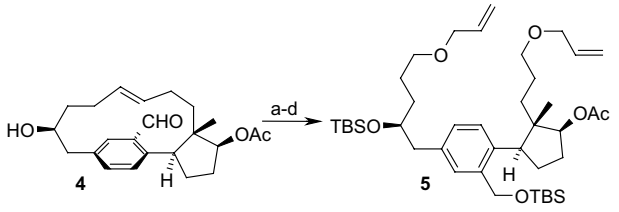
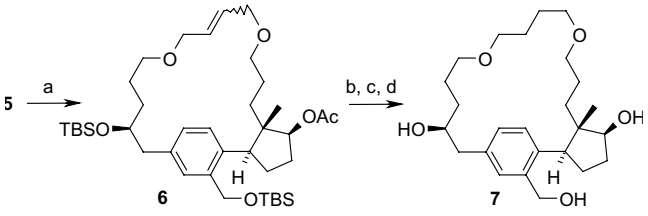
Table 1. Metathesis reactions via Figure 1

Entry	Olefin	R1	R2	Cat[a]	Condition	Yield (%)
1	**5**	$CH_2Oallyl$	$CH_2Oallyl$	A	DCM, rt, 6.5 h	36
2	**8a**	$CH_2Oacryl$	$CH_2Oacryl$	A	DCM, rt, 2 d	—
3	**8a**	$CH_2Oacryl$	$CH_2Oacryl$	B	DCM, rt, 2 d	69
4	**8b**	CHMeOallyl	CO_2allyl	B	DCM, rt, 2 d	34
5	**8b**	CHMeOallyl	CO_2allyl	B	DCM, Δ, 4 h	73
6	**8c**	CHMeOallyl	CO_2CH_2allyl	B	DCM, Δ, 4 h	70
7	**8d**	CHMeOallyl	$CO_2(CH_2)_2allyl$	B	DCM, Δ, 4 h	34
8	**8e**	$CMe{=}CH_2$	CO_2CH_2allyl	B	DCM, Δ, 1 h	—
9	**8e**	$CMe{=}CH_2$	CO_2CH_2allyl	B	MePh, Δ, 4 h	20

[a] A = $RuCl_2(PCy_3)_2{=}CHCHCMe_2$, B = $(IMES)(PCy_3)Cl_2Ru{=}CHPh$; IMES = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.



Scheme 2. (a) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C, 40 min; (b) TBSCl, imidazole, DMAP, 4 Å molecular sieves, CH_2Cl_2, 90%; (c) O_3, CH_2Cl_2, MeOH, −78 °C, 3 min, $NaBH_4$, EtOH, 0 °C, 1 h, 82%; (d) allylbromide, $NBu_4^+HSO_4^-$, NaOH, toluene, H_2O, rt, 6 h, 80%.



Scheme 3. (a) $(PCy_3)_2Cl_2Ru{=}CHPh$ = Grubbs catalyst, first generation,[6] CH_2Cl_2, rt, 6.5 h, 36%; (b) H_2/Pd–C/Na_2CO_3, EtOAc; (c) NaOMe, 5% in MeOH; (d) CSA, CH_2Cl_2/MeOH 1:1, 50% (three steps).

macrocycle **6** within 4 h (36% yield, mixture of *E*/*Z*-isomers) (Scheme 3). Hydrogenation of the double bond and subsequent cleavage of the protecting groups gave the saturated macrocycle **7**.†

To show that this ring enlargement is generally applicable, different types of olefins were subjected to the metathesis reaction (Fig. 1 and Table 1). The dienes **8a–e** were synthesized in a similar fashion to **5**. The more reactive Grubbs catalyst of the second generation[7] was necessary to obtain the desired product starting

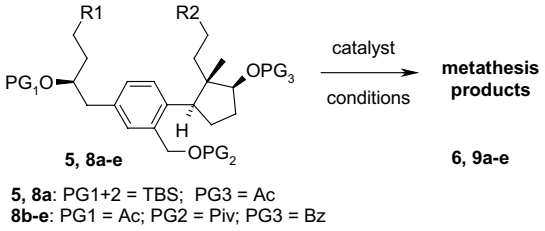


Figure 1. Metathesis reactions (Table 1).

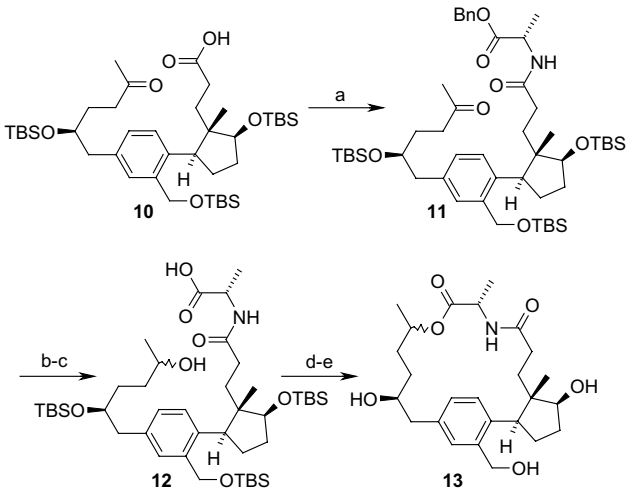
with bisacrylester **8a** (Table 1, entries 2 and 3). The yield of the cyclization product of **8b** was improved by increasing the temperature (Table 1, entries 4 and 5). Cyclization of **8c** and **8d** having an allylether and an homoallylester or 4-pentenester moiety could only be accomplished at reflux temperature in dichloromethane (Table 1, entries 6 and 7). Even higher temperature (refluxing toluene) had to be applied for the combinations of the methylallyl and homoallyl structures in **8e** (Table 1, entries 8 and 9). All metathesis products were obtained as mixtures of *E*/*Z*-isomers.

Our second approach towards more flexible novel templates is based on the incorporation of amino acids. This allows the introduction of a broad variety of functional groups as well as the modification of the lipophilicity of the molecule. Compound **13** with an incorporated alanine linker was synthesized as a prototype, starting from **10**.[8] First an amidation with alanine benzyl ester afforded **11** in 47% yield. Reduction of the keto group in **11** followed by deprotection of the carboxylic acid moiety gave **12** as a mixture of epimers. Macrocyclization using Yamaguchi conditions and cleavage of the three silyl ethers in the presence of camphorsulfonic acid led finally to the fully deprotected 18-membered macrocycle **13** (Scheme 4).‡

In summary, we have presented a novel approach to new conformationally flexible and highly functionalized macrocycles derived from steroids. These macrocycles can now be exploited for the generation of diverse compound libraries.

† Selected analytical data for compound **7**: ^1H NMR ($CDCl_3$): δ = 0.88 (s, 3H), 1.28–1.75 (m, 12H), 1.78–1.99 (m, 2H), 2.10–2.25 (m, 2H), 2.70 (dd, *J* = 7/14 Hz, 1H), 2.93 (dd, *J* = 5/14 Hz, 1H), 3.15–3.44 (m, 8H), 3.45–3.52 (m, 1H), 3.90–4.02 (m, 2H), 4.62 (d, *J* = 13 Hz, 1H), 4.75 (d, *J* = 13 Hz, 1H), 7.06 (dd, *J* = 2/8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 1H), 7.30 (d, *J* = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 24.8, 26.2, 26.7, 27.0, 28.2, 30.7, 33.2, 35.3, 43.3, 44.5, 47.7, 63.2, 70.1, 70.8, 70.8, 71.1, 71.3, 79.9, 128.8, 128.9, 130.2, 136.1, 137.5, 140.4; MS (ESI): *m*/*z* = 421 [M+1], 438 [M+18].

‡ Selected analytical data for compound **13**: MS (Cl–NH_3): *m*/*z* = 448 [$M+H^+$], 465 [$M+NH_4^+$].



Scheme 4. (a) EDC, hydroxybenzotriazole, L-alanine benzylester, Et_3N, 47%; (b) $NaBH_4$, CH_2Cl_2, MeOH; (c) H_2/Pd–C, CF_3CH_2OH, Na_2CO_3, quant.; (d) 2,4,6-trichlorobenzoylchloride, Et_3N, THF, DMAP, toluene, rt, 2 h; (e) CSA.

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8. **10** was synthesized in a similar way to **5**.