Synthesis of Ansa-Bridged Macrocyclic Lactams Related to the Antitumor Antibiotic Geldanamycin by Ring Closing Metathesis

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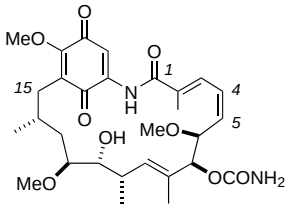
Dedicated to Professor Hans J. Schäfer on the occasion of his 65th birthday

Abstract: The α,β,γ,δ-unsaturated 2,4,5-trimethoxyanilides **8a**–**e** which bear a terminal alkenyl side chain at the 3-position were prepared from 1,2,4-trimethoxybenzene (**2**) in four steps and 25–41% overall yield. Attempted ring closing metathesis reactions were successful in the presence of catalysts **9** for the substrates **8c**–**e** and led to the products **10c**–**e** (66–91% yield). Substrates **8a** and **8b** with a shorter alkenyl side chain did not cyclize.

Key words: arenes, antitumor agents, macrocycles, metathesis, ring closure

Geldanamycin (**1**) (Figure) is an ansamycin antibiotic which was isolated from *Streptomyces hygroscopicus* var. *geldanus* var. *nova* (UC-5208).[1] The compound has recently attracted considerable attention due to its antitumor activity.[2] A derivative of geldanamycin, 17-allylamino-17-demethoxygeldanamycin, awaits phase II clinical trials as an antitumor agent.[3] The mechanism of action in cells is based on an inhibition of nucleotide binding to the molecular chaperone heat shock proteine (Hsp) 90.[4,5] Additional studies suggest that the binding to Hsp90 is not the only cellular interaction responsible for the observed activity.[6] The biological importance of geldanamycin makes itself and simpler analogs thereof interesting target compounds for *de novo* synthesis.[7,8] Structurally, geldanamycin is related to the ansamycin antibiotics macbecin I[9] and herbimycin A[10] syntheses of which have been previously reported. The macrolactam ring of these compounds has been formed by conventional macrolactamization.



Geldanamycin (**1**)

Figure

We envisioned the ring closing metathesis[11] of a suitable 1,ω-diene to be a new and general approach to the geldanamycin skeleton. The prerequisite starting material bears a 2-methylpenta-2,4-dienoic acid anilide the terminal double of which would undergo the metathesis reaction with an internal terminal alkene. As literature precedent for such a metathesis was rare[12,13] we undertook model studies the preliminary results of which are reported in this communication.

The synthesis of the metathesis precursors (Scheme) commenced with the alkylation of 3-lithiated 1,2,4-trimethoxybenzene (**2**).[7] The required iodides **3** were prepared by conventional methods from the corresponding bromides (**3a**, n = 1; NaI in acetone) or alcohols (**3b**–**e**, n = 2–5; PPh_3, I_2, imidazole in benzene). The chain length was varied in order to evaluate its influence on the success of the ring closing metathesis. After regioselective nitration of the arene products **4** to the nitroarenes **5** a reduction with tin in aqueous hydrochloric acid delivered the anilines **6**. The acylation of anilines with 2-methylpenta-2,4-dienoic acid (**7**) or its derivatives turned out to be delicate. An extensive and careful optimization of the reaction conditions was necessary to ensure a selective and smooth conversion to the anilides **8**. The best conditions we found are based on the use of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as activating agent and 1-hydroxy-7-azabenzotriazole (HOAt) as promoter for the acylation.[14] Acid **7** was in turn obtained from acrolein and the triphenylphosphonium salt derived from methyl 2-bromopropionate[15] by a Wittig reaction and subsequent saponification (NaOH in MeOH). The yields for the individual steps of the sequence **3** → **8** are summarized in Table 1.

Metathesis reactions were carried out with the first generation Grubbs's catalysts **9a**[16] and **9b** which is commercially available and with the more recently described catalyst tricyclohexylphosphine[1,3-dimesityl-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium dichloride (**9c**).[17] Relevant results are summarized in Table 2. Initial studies which were conducted with compound **8c** (n = 3) at relatively high concentrations (6 mM) were disappointing as they delivered the desired product only in low yields and as several side products were formed (entry 1). The addition of $Ti(i\text{-}PrO)_4$[18] to the reaction mixture had no benefical impact in this case. A decrease of the concentration gave a cleaner conversion although even at 2 mM a significant amount of dimerization was observed (entry 2). At a concentration of 0.5 mM the dimer formation was almost completely suppressed (entry 3). Application of these

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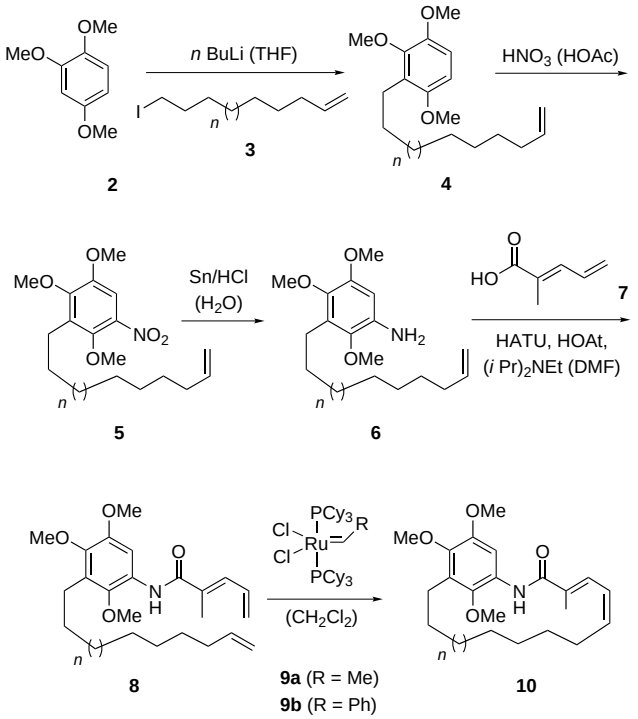

Scheme

Table 1 Yields of Isolated Products for the Four Individual Steps in the Conversion of Arene **2** to the Metathesis Precursors **8a–e** (cf. Scheme)

n	Iodide	Yield[a] **4** [%]	Yield[b] **5** [%]	Yield[c] **6** [%]	Yield[d] **8** [%]
1	**3a**	59	73	82	72
2	**3b**	76	95	77	58
3	**3c**	76	98	84	66
4	**3d**	69	95	79	68
5	**3e**	73	94	83	63

[a] Conditions: **2**, BuLi (1.1 equiv) in THF, r.t., 45 min, then **3**, 0 °C, 14 h.
[b] Conditions: HNO_3 (5.7 equiv) in HOAc, r.t., 2 h.
[c] Conditions: Sn (8 equiv) in aq HCl, 60 °C, 1 h. In some runs, addition of HCl to the double bond was observed as a side reaction.
[d] Conditions: **7** (1 equiv), HATU (1 equiv), HOAt (1 equiv), *i*-Pr_2NEt (2.5 equiv) in DMF, 0 °C → r.t., 2 d.

conditions to the starting materials **8d** and **8e** with a longer chain (n = 4, 5) was even more rewarding (entries 4 and 6). The addition of catalyst after a reaction time of 18 h proved advantageous (entries 5 and 9) to drive the reaction to completion. The source of catalyst itself turned out to be less important for the success of the reaction (entries 6–8). The benzylidene catalyst **9b** appears slightly superior as compared to **9a** and **9c**. Triene **8b** with a shorter chain (n = 2) did not give any cyclisation product at all (entry 10). After prolonged heating some dimer and unreacted starting material were observed. Apparently, the increased strain in the corresponding medium-sized ring prohibits cyclization. Reactions with substrate **8a** remained also unsuccessful (entry 11).

Table 2 Attempted Ring Closing Metathesis of Precursors **8a–e** (cf. Scheme) Under a Variety of Conditions[19]

Entry	Substrate	Conc. [mM]	Catalyst[a]	Time[b] [h]	Product	Yield[c] [%]
1	**8c**	6	**9a**	20	**10c**	14
2	**8c**	2	**9a**	20	**10c**	44[d]
3	**8c**	0.5	**9a**	20	**10c**	66[e]
4	**8d**	0.5	**9a**	36	**10d**	77[f]
5	**8d**	0.5	**9b**	36[g]	**10d**	85
6	**8e**	0.5	**9a**	36	**10e**	77[h]
7	**8e**	0.5	**9b**	36	**10e**	91
8	**8e**	0.5	**9c**	36	**10e**	70[i]
9	**8e**	0.5	**9a**	36[g]	**10e**	87
10	**8b**	0.5	**9a**	60	**10b**	–[j]
11	**8a**	0.5	**9a**	40	**10a**	–[k]

[a] 10 mol% of the catalyst was employed unless otherwise stated.
[b] Time after which the reaction (reflux in CH_2Cl_2) was stopped.
[c] Yield of isolated product.
[d] Starting material (4%) and dimer (36%) were also isolated.
[e] Starting material (14%) was also isolated, minor dimer formation was observed.
[f] Minor dimer formation was observed.
[g] After 18 h at reflux additional 5 mol% of the catalyst were added.
[h] Starting material (8%) was also isolated.
[i] Starting material (15%) was also isolated.
[j] Only starting material (50%) and dimer/oligomer (25%) were isolated.
[k] Only starting material (84%) and dimer/oligomer (10%) were isolated.

The double bond formed in the course of the metathesis reactions is uniformly configurated. ^{1}H NMR NOESY experiments with compound **10e** confirmed the expected (*Z*)-configuration which is also found in geldanamycin (C-4/C-5). Attempts to oxidize the products of the metathesis to the corresponding methoxy benzoquinones are currently underway as are biological tests of the products.

In summary, we have shown that the ring closing metathesis is a viable pathway for the synthesis of ansa-bridged macrocyclic lactams. Under high dilution conditions the reaction proceeds cleanly and in good yields. The application of this strategy to structurally more complex macrocyclic lactams is currently being pursued in our laboratory.

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(19) Representative procedure for the ring closing metathesis **8** → **10**: A solution of anilide (**8d**, 50 mg, 113 μmol) in 5 mL of dichloromethane was slowly added to a refluxing solution of Grubbs's catalyst (**9a**, 8.6 mg, 11.3 μmol) in 220 mL of dichloromethane. After 36 h at reflux, the reaction mixture was cooled and the solvent was removed in vacuo. The residue was purified by flash chromatography (pentane/EtOAc = 9:1). Compound **10d** (36 mg, 87 μmol, 77%) was obtained as a colorless liquid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.10–1.47 (m, 2 H), 1.65–1.68 (m, 2 H), 2.04 (d, *J* = 0.7 Hz, 3 H), 2.21 (virt. q, *J* ≅ 8.0 Hz, 2 H), 2.70 (t, *J* = 6.5 Hz, 2 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 5.96 (virt. q, *J* ≅ 9.1 Hz, 1 H), 6.32 (virt. t, *J* ≅ 10.9 Hz, 1 H), 6.99 (d, *J* = 11.3 Hz, 1 H), 7.95 (s, 1 H), 8.23 (s br, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 12.6, 22.4, 27.2, 27.4, 28.1, 28.5, 28.6, 28.8, 29.4, 29.6, 29.7, 55.9, 60.9, 61.3, 101.4, 124.1, 126.7, 127.6, 128.8, 133.5, 137.9, 141.2, 143.3, 149.4, 168.4.