Asymmetric Total Synthesis of Attenol A and B

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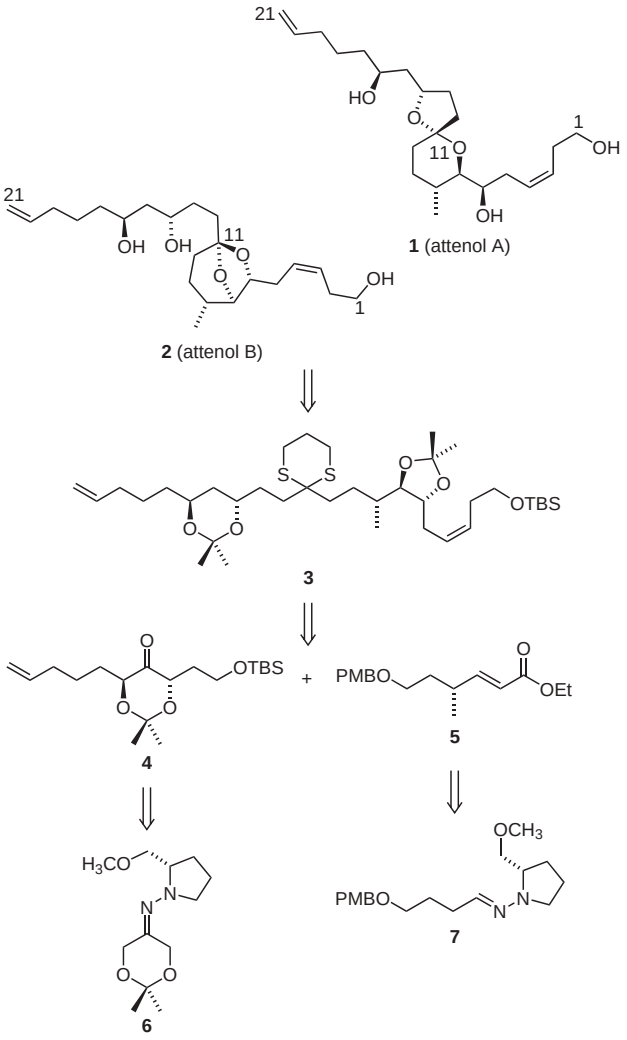
Abstract: The asymmetric total synthesis of attenol A (**1**) and B (**2**), which possess challenging structures and an interesting biological activity, was accomplished in a convergent and highly stereoselective manner (de, ee ≥ 96%) with good overall yield. The short total synthesis is based on asymmetric alkylations of SAMP-hydrazones as well as a Sharpless asymmetric dihydroxylation as key steps.

Key words: asymmetric dihydroxylation, dithianes, natural products, SAMP-hydrazone methodology, total synthesis

Both attenol A (**1**) and attenol B (**2**, Scheme 1) are marine natural products, which were isolated in 1999 from the Chinese bivalve *Pinna attenuata* by Uemura and coworkers.[1] They are isomeric triols differing from each other only by which hydroxyl groups are involved in the ketal formation. This results in a 1,6-dioxa-spiro[4.5]decane and a 6,8-dioxabicyclo[3.2.1]octane unit as the main structural feature of attenol A and B, respectively. In preliminary biological studies both compounds exhibited moderate cytotoxicity against P388 cells (**1**: IC_{50} = 24 μg mL^{-1}; **2**: IC_{50} = 12 μg mL^{-1}).[1] Due to their interesting biological activity and their natural scarcity, these marine natural products have attracted considerable interest as synthetic targets. Uemura, Suenaga et al.[2a,b] successfully carried out the first total synthesis of attenol A and B followed by Eustache, Van de Weghe et al.[2c] (attenol A). We now wish to report the results of our approach leading to a very efficient, asymmetric total synthesis of attenol A and B, which augurs well for the future synthesis of stereoisomers and derivatives of these compounds for further biological studies.

As depicted in Scheme 1, our synthesis focused on the generation of dithiane **3**,[3] which - after thioketal cleavage and acid-catalyzed ketalization – would lead to both attenol A and B.[4] The *anti*-2,2-dimethyl-1,3-dioxan-5-one **4** and the α,β-unsaturated ester **5** were thought to be appropriate precursors for electrophiles required in the construction of **3**. It would be effective to synthesize **4** and **5** by means of asymmetric alkylation using the SAMP-hydrazone methodology (**6** and **7**, respectively), as all three stereocenters would be generated by using a single commercially available chiral auxiliary.[5]

As outlined in Scheme 1 and Scheme 2, our synthesis of the *anti*-2,2-dimethyl-1,3-dioxane fragment of **3** started from 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone (**6**).[6] Successive alkylation of **6** with (2-bromoethoxy)-*tert*-butyldimethylsilane[7] and 5-bromopent-1-ene generated the bisalkylated SAMP-hydrazone **8** with de ≥ 96%. Oxalic acid hydrazone cleavage gave **4** in 75% yield over three steps and de, ee ≥ 96%.[8,9]



Scheme 1 Retrosynthetic analysis of attenol A and B.

Following the observations of Barton and McCombie[10] and in addition to the knowledge acquired in our group,[11] it was assumed that the most efficient way to remove the keto group of *anti*-2,2-dimethyl-1,3-dioxan-5-one (**4**) would be via a sequence of reduction and radical deoxygenation. Therefore xanthate **9** was synthesized (96% yield over two steps, de = 23%).[12]

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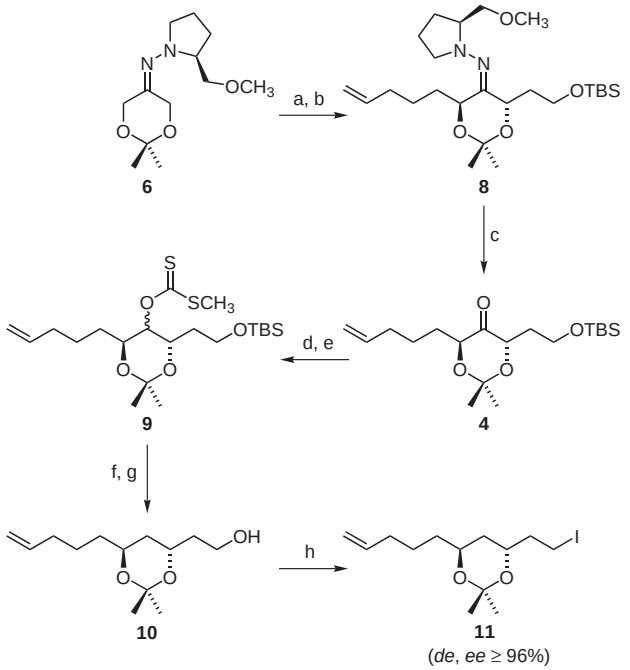
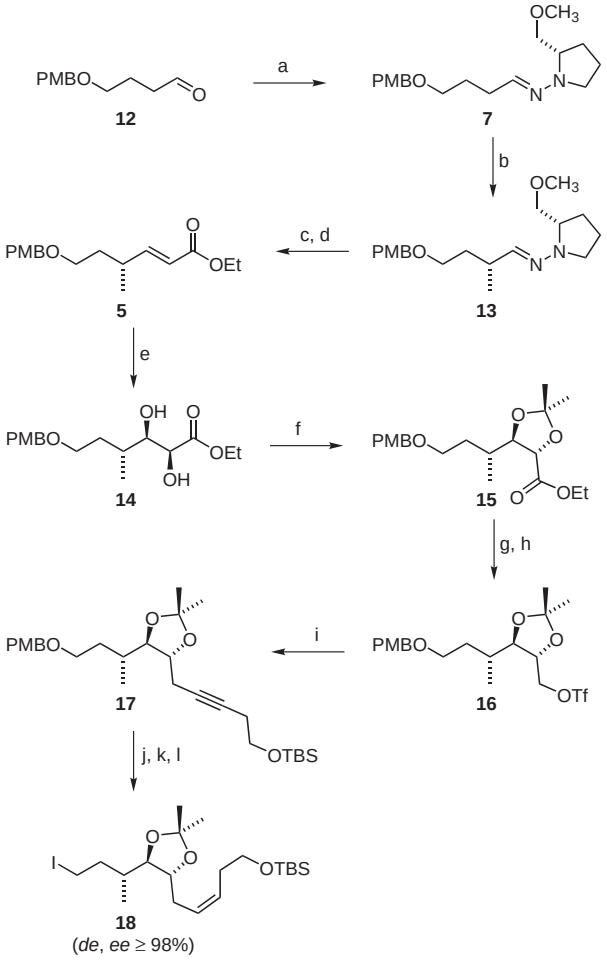


Scheme 2 *Reagents and conditions*: (a) *t*-BuLi, THF, –78 °C, then (2-bromoethoxy)-*tert*-butyldimethylsilane, –100 °C → 25 °C; (b) *t*-BuLi, THF, –78 °C, then 5-bromopent-1-ene, –100 °C → 25 °C; (c) sat. oxalic acid, Et_2O, 25 °C, 75% over three steps; (d) $NaBH_4$, MeOH, 0 °C; (e) NaH, THF, CS_2, MeI, 0 °C → 25 °C, 96% over two steps; (f) Bu_3SnH, AIBN (cat.), toluene, reflux; (g) TBAF, THF, 25 °C, 91% over two steps; (h) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0 °C, 94%.

The radical reduction using Bu_3SnH and a catalytic amount of AIBN in refluxing toluene and subsequent cleavage of the TBS ether yielded alcohol **10** (91% yield over two steps).[13] Iodination of this alcohol gave iodide **11** (94%), the first of the two electrophiles which had to be coupled by the Corey–Seebach reaction.

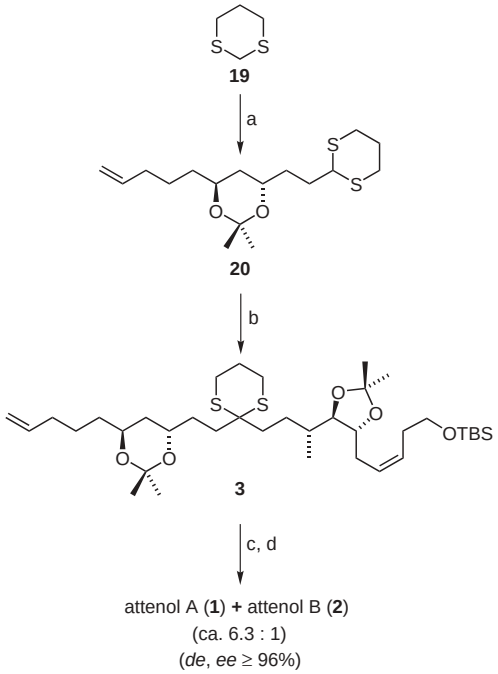
As shown in Scheme 3, the synthesis of the second electrophile **18** started from 4-(4-methoxybenzyloxy)-butyraldehyde (**12**).[14] Condensation with SAMP, resulting in the corresponding hydrazone **7** (95%), followed by alkylation with MeI yielded **13** in 86% yield and de = 96%.[15] Ozonolytic cleavage of the hydrazone and Wittig olefination led to **5** with a small loss of optical purity (71%, ee = 92%).[15] Subsequent Sharpless asymmetric dihydroxylation proceeded smoothly (96%) to give a mixture of two diastereomers whose de corresponded to the ee of the unsaturated ester **5**.[16] After acetonide formation with *p*-toluenesulfonic acid in 2,2-dimethoxypropane (94%) the minor diastereomer could be separated by HPLC yielding **15** with de, ee ≥ 98%.[17,18] The alcohol obtained after reduction of the ester moiety with lithium aluminum hydride (95%) was activated as its triflate derivative **16**. Displacement with lithiated *tert*-butylbut-3-ynyloxydimethylsilane[19] gave **17** (89% yield over two steps). Lindlar reduction, followed by the cleavage of the *p*-methoxybenzyl ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and iodination of the generated alcohol afforded **18** (77% yield over three steps).



Scheme 3 *Reagents and conditions*: (a) SAMP, Et_2O, 0 °C to 25 °C, 95%; (b) LDA, THF, 0 °C, then MeI, –120 °C to 25 °C, 86%; (c) O_3, CH_2Cl_2, –78 °C; (d) Ph_3PCHCO_2Et, CH_2Cl_2, 25 °C, 71% over two steps; (e) AD-mix β, $MeSO_2NH_2$, *t*-BuOH:H_2O = 1:1, 0 °C, 96%; (f) 2,2-DMP, PTSA (cat.), 25 °C, 94%; (g) LAH, Et_2O, 0 °C, 95%; (h) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, –40 °C to –30 °C; (i) *tert*-butylbut-3-ynyloxydimethylsilane, *t*-BuLi, THF, DMPU, –78 °C, then **16**, –78 °C to 25 °C, 89% over two steps; (j) H_2, Lindlar catalyst, MeOH, 25 °C, 94%; (k) DDQ, CH_2Cl_2, 25 °C, 99%; (l) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0 °C, 83%.

With both electrophiles **11** and **18** in hand, the synthesis of both attenols was accomplished as shown in Scheme 4. The alkylation of dithiane **19** with **11** proceeded cleanly in 96% yield. The second alkylation using **18** yielded **3** (84%). Copper mediated hydrolysis of this dithiane and *p*-toluenesulfonic acid catalyzed ketal formation finally gave a mixture of the title compounds **1** (57%) and **2** (9%, each over two steps).[20]

In summary, we have demonstrated a very efficient and highly stereoselective synthesis of attenol A and B employing asymmetric alkylations of SAMP-hydrazones as well as a Sharpless asymmetric dihydroxylation as key steps in order to install all the stereocenters apart from C-11, which was formed in the acid catalyzed cyclization step. The synthesis proceeded in 15 steps from **12** (longest linear sequence) and 19% overall yield and is not only the shortest but also the most efficient synthesis so far.



Scheme 4 *Reagents and conditions*: (a) **19**, *t*-BuLi, THF, DMPU, –78 °C, then **11**, 96%; (b) **20**, *t*-BuLi, THF, HMPA, –78 °C, then **18**, –78 °C to 25 °C, 84%; (c) CuO, $CuCl_2$, aq acetone; (d) PTSA, MeOH, 25 °C, 66% over two steps.

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(9) Since the hydrazone cleavage of **8** proceeded without epimerisation, the ee of the *anti*-2,2-dimethyl-1,3-dioxan-5-one **4** is assumed to be at least as high as its de. The absence of epimerization can be proved on the stage of the *anti*-2,2-dimethyl-1,3-dioxane **10**, whose ^{13}C NMR resonance is at δ = 100.2 in accordance to Rychnovsky's criteria. See: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
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(12) Experiments towards higher stereoselectivities in the reduction step were not conducted since the newly formed stereogenic center had to be removed afterwards.
(13) A large excess of Bu_3SnH was necessary to sufficiently reduce the occuring side reactions. Under optimized conditions **10** contained only 3 mol% of an isomerization product in which the terminal double bond had migrated between C-19 and C-20 (the numbering refers to the final natural products).
(14) Ishikawa, T.; Ikeda, S.; Ibe, M.; Saito, S. *Tetrahedron* **1998**, *54*, 5869.
(15) The de of **13** and the ee of **5** were verified by HPLC on chiral stationary phase. In order to do so, the 1:1-epimeric mixture of **13** and the racemate of **5** had to be synthesized which was performed starting from the *N,N*-dimethyl-hydrazone of **12**. Alkylation with MeI and ozonolysis gave the α-alkylated racemic aldehyde which was treated with SAMP and Ph_3PCHCO_2Et to obtain the desired mixtures of compounds.
(16) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(17) The ee of **15** was verified by HPLC on chiral stationary phase. For this, *ent*-**15** had to be synthesized analogously to **15** starting from the RAMP-hydrazone *ent*-**7** and performing the Sharpless asymmetric dihydroxylation of *ent*-**5** with the AD-mix α.
(18) The reaction sequence leading to **15** was also conducted starting with **5** of much lower enantiomeric purity (i.e. ee = 83%). After HPLC, **15** (obtained in lower yield) was still diastereomerically and enantiomerically pure (de, ee ≥ 98%) which indicates the high stereoselectivity of the Sharpless asymmetric dihydroxylation.
(19) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; He, C. H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.
(20) Our synthetic material was identical in all respects with physical and spectroscopic data provided for the natural products. Compound **1**: $[\alpha]_D^{26}$ –8.2 (*c* 0.35, $CHCl_3$) {(ref.[2a], $[\alpha]_D^{28}$ –9.7 (*c* 0.35, $CHCl_3$) and $[\alpha]_D^{28}$ –8.0 (*c* 0.38, $CHCl_3$) for natural **1**. Compound **2**: $[\alpha]_D^{26}$ 37 (*c* 0.072, $CHCl_3$) {(ref.[2a], $[\alpha]_D^{29}$ 34 (*c* 0.073, $CHCl_3$) and $[\alpha]_D^{28}$ 31 (*c* 0.065, $CHCl_3$) for natural **2**}.
All new compounds gave satisfactory spectral data and correct elemental analyses.