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Silicon Tether-Aided Coupling Metathesis: Application to the Synthesis of Attenol A

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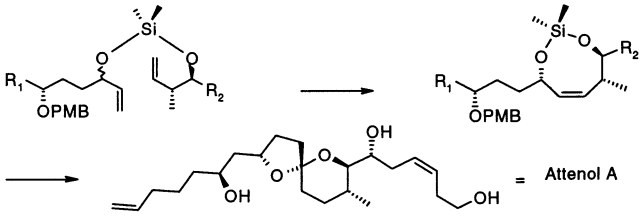
ABSTRACT

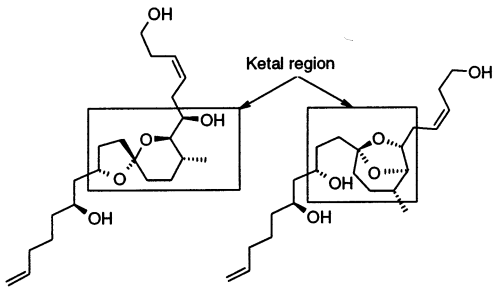


A new synthesis of attenol A is described. Key features of this work include a crucial silicon tether-aided coupling metathesis step and the use of iodoetherification as an efficient protection method for 1,5-ene-ols.

Attenols A (**1**) and B have been recently isolated and characterized[1] and then synthesized[2] by Uemura. These compounds, which exhibit moderate cytotoxicity against P388 cells (IC_{50} are 24 and 12 μg/mL for attenols A and B, respectively), only differ in the "ketal region", attenol A featuring a [5,4] spiroketal moiety and attenol B containing a dioxa-bicyclo[3.2.1]octane unit. Attenols are densely functionalized, asymmetric molecules, and their preparation poses interesting challenges to synthetic organic chemists, as nicely illustrated by Uemura et al.[2] In the present paper, we wish to present an alternative approach to attenol A, which relies on our recently developed metathesis-based synthesis of spiroketals.[3]

Our strategy is depicted in Scheme 1. After an initial obvious disconnection between C-5 and C-6,[4] the spiroketal moiety of attenol A can be considered to result from cyclization of a ketone-diol, itself readily obtained via silicon-tethered ring-closing metathesis of two fragments.[5] Fragment A (**2**) was readily prepared from (*tert*-butyl-diphenyl-silyloxy)-acetaldehyde according to Oikawa.[6] According to our plans, PG_1 was to be removed after assembling the whole sensitive attenol A skeleton. This led us to select TPS as a protecting group because of its insensitivity to mild basic or acidic conditions and its facile cleavage by fluoride ion.

The synthesis of fragment B looked more problematic (and lengthy) until we realized that it could be derived from a chiral, C_2 symmetrical diol (**4**), itself obtainable from the



Attenol A (**1**) Attenol B

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(1) Takada, N.; Suenaga, K.; Yamada, K.; Zheng, S.-Z.; Chen, H.-S.; Uemura, D. *Chem. Lett.* **1999**, 1025−1026.

(2) (a) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527−529. (b) Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983−1995.

(3) Boiteau, J.-G.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 239−242.

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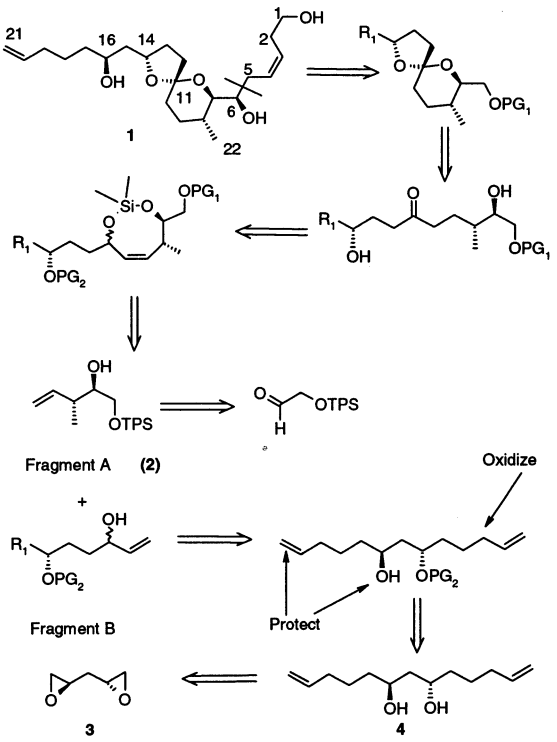
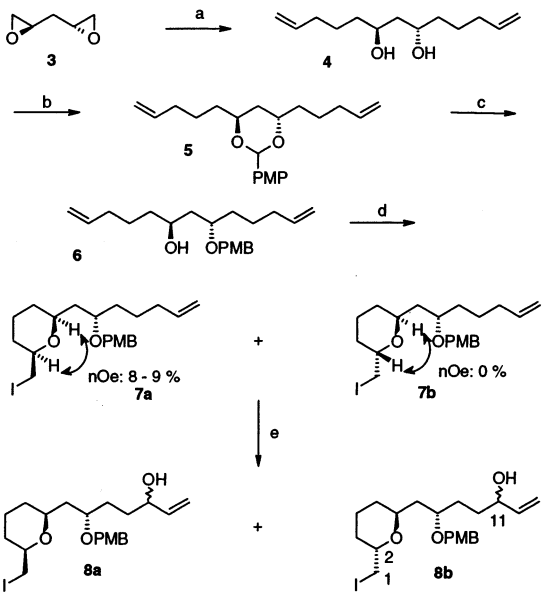
Scheme 1



Scheme 2 [a]

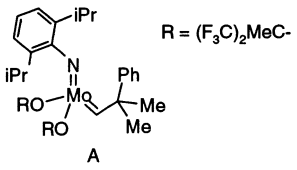


[a] (a) CH_2=$CHCH_2CH_2MgBr$/CuI, THF, −40 °C, 3.5 h, 88%; (b) $PMPCH(OMe)_2$, CSA (cat.), CH_2Cl_2, 16 h, 20 °C, 88%; (c) $NaBH_3CN$, CF_3COOH, DMF, 0 °C, 10 h, 76%; (d) NIS, K_2CO_3, CH_2Cl_2, 20 °C, 16 h, 80%; (e) SeO_2/TBHP, CH_2Cl_2, 20 °C, 12 d, 68%.

known diepoxide **3**.[7] Obviously the key problem in this approach was the differentiation of the two olefinic double bonds in monoprotected **4**. One of them had to be oxidized at the allylic position to provide an anchor for the silicon tether, while the other had to be masked in order not to interfer with the desired RCM. With respect to the planned sequence, enantioselectivity of the allylic oxidation step did not appear to be an issue, as the hydroxyl was to be oxidized to the corresponding ketone after RCM. The practical realization of this approach is shown in Scheme 2. Thus, allylmagnesiumbromide/cuprous iodide opening of diepoxide **3** gave chiral diol **4**,[8] which was readily converted to ketal **5**. Reduction ($NaBH_3CN$, CF_3COOH) afforded the corresponding *p*-methoxybenzyl ether **6**.

The 1,5 relationship between the free hydroxyl and one of the double bonds in **6** suggested that both functions could be protected in a single step by electrophile-induced cyclic ether formation. Among the various electrophiles we used, NIS worked best, leading to pyrane derivatives **7a** and **7b** in good yield (**7a**/**7b**, 7:3).[9] Although there are many examples of halogenoetherification in the literature, we are aware of only one instance of its use for protection purposes.[10] A matter of concern, in our case, was the sensitivity of the primary iodide, which had to withstand the various reaction conditions encountered along the succession of steps leading to attenol. Optimizing the last reaction of the sequence, the allylic oxidation of the remaining olefinic double bond in **7**, required extensive experimentation, but we were rewarded by finally finding the conditions for reliable conversion of **7** into **8**. Although the reaction is slow, it is very easy to perform and repeatedly affords good yield of allylic alcohols as a 1:1 mixture of *R* and *S* isomers at the newly formed chiral carbon atom.

With fragments A and B in hand, we proceeded to the key coupling/RCM sequence (Scheme 3). Treatment of **2** by dichlorodimethylsilane and addition of the resulting crude chloro-dimethylsilyl ether to allylic alcohols **8a,b** gave the mixture of silylketals **9** in high yield, which was submitted to RCM conditions using the molybdenum complex A (Schrock complex = [Mo]) as catalyst.



A

(4) Attenol is numbered as indicated in Scheme 1 (starting from the "right end" ot the molecule). To have a consistent numbering for all synthetic intermediates, however, these are numbered starting from the "left end" of the molecule as shown in Schemes 2 and 3.

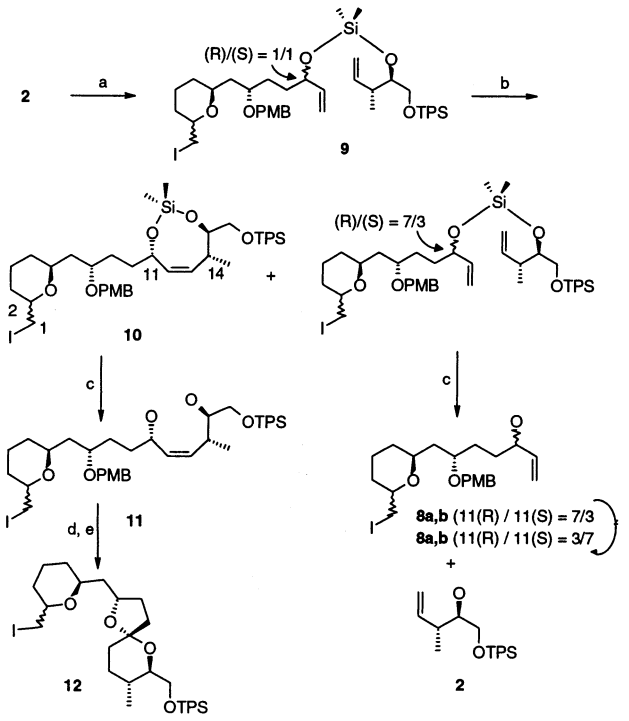
(5) For previous examples of silicon-tethered ring-closing metathesis, see: (a) Evans P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769. (b) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429−1432. (c) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517−1519. (d) Gierash, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999−4000. (e) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *2*, 2157−2159.

(6) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048−5068.

(7) Rychnovsky, S. D.; Griesgraber, G. Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161−5169.

(8) NMR data and optical rotation of diol **4** were in perfect agreement with those of **ent-4** (Hoffmann, R. W. Colin, K. B.; Schifer, J.; Fleischhauer, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407−2414).

Scheme 3 [a]

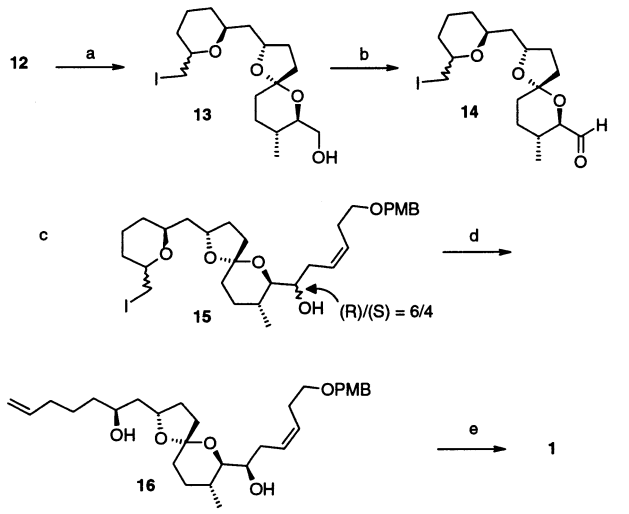


[a] (a) (i) BuLi, THF, −78 °C, 10 min, then Me_2SiCl_2 (excess), −78 → 20 °C, 1 h, (ii) **8a,b**, imidazole, THF, 20 °C, 16 h, 92%; (b) [Mo], benzene, 20 °C, 24 h; (c) TFA, THF, MeOH, 20 °C, 24 h, 22% (**11**, 2 steps), 30% (**8**, two steps), 45% (**2**, 2 steps); (d) MnO_2 (30 equiv), AcOEt, rt, 24 h; (e) (i) H_2 Pd/C, AcOEt, rt, 4 h, (ii) DDQ, CH_2Cl_2, H_2O, 20 °C, 30 min, 72% (3 steps); (f) (i) *p*NO_2BzCOOH, PPh_3, DEAD, −20 °C, 2 h, (ii) NaOH,EtOH, 0 → 20 °C, 2 h, 80% (2 steps).

We observed a partial conversion and the formation of only two out of four possible isomers of **10**. The strong NOE effect between H_{11} and H_{14} showed that both protons in **10** were axially oriented, implying that the RCM products had the 11(*S*) configuration as shown in Scheme 2. In contrast to previous results[3] in a similar case, where the different reactivity of stereoisomers toward RCM could be overcome, here we were unable to force the reaction to go to completion. Thus, although the stereochemistry at C11 is irrelevant with respect to the planned sequence of reactions (as the next step destroys this asymmetric center), in our case it proved to be crucial for the success of the metathesis step. This limitation could be partially overcome as follows: isolation of unreacted **9** and quantitative cleavage of the silyl bridge afforded **8a,b** as a mixture containing mainly 11(*R*) **8a,b** This was cleanly converted into a mixture containing mainly 11(*S*) **8a,b** by Mitsunobu reaction (overall yield 80%), which can be recycled. Cleavage of the silylketal in **10** afforded diol **11** (22% yield from **9**), which was converted to the key intermediate **12** in good (72%) yield, by oxidation of the allylic alcohol, reduction of the conjugated double bond, and oxidative removal of the PMB protective group with concomitant ketal formation.

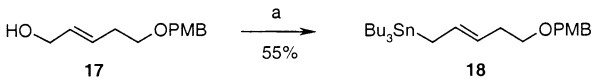
Intermediate **12** was converted to attenol A as shown in Scheme 4.

Scheme 4 [a]



[a] (a) TBAF (1.2 equiv), THF, 20 °C, 24 h, 80%; (b) Dess−Martin periodinane, pyridine, CH_2Cl_2, 20 °C, 2.5 h; (c) (*E*)-Bu_3SnCH_2−CH═CH−CH_2CH_2OPMB, $SnCl_4$, CH_2Cl_2, −78 °C, **15** (16(*R*)) 35% and **15** (16(*S*)) 30% (2 steps); (d) BuLi, 3 equiv, −78 °C, 3 h, 60% (25% **15** recovered); (e) DDQ, CH_2Cl_2, H_2O, 20 °C, 30 min, 60%.

Removal of the TPS protective group and Dess−Martin oxidation[11] of the resulting primary alcohol produced the crude sensitive aldehyde **14,** which was directly used for the next step. $SnCl_4$-catalyzed reaction[12] with stannyl derivative **18** prepared from the known (*E*)-5-(4-methoxybenzyloxy)-pent-2-en-1-ol (**17**)[13] according to Brückner[14] afforded **15** as a ca. 6:4 mixture of 16(*R*) and 16(*S*) isomers, which could be separated by chromatography.



17 18

(i) n-BuLi, THF, -78°C, 20 min (ii) MsCl, THF, -78°C, 30 min (iii) Bu_3SnLi, THF, -78°C to 20°C, 16 h.

These results deserve some comments. Asymmetric δ-methyl, ϵ-benzyloxyallylstannanes, in the presence of $SnCl_4$, are known to react with aldehydes with very high regio- and stereoselectivity to afford *anti*-homoallylic alcohols in which the olefinic double bond is exclusively *cis*.

According to the mechanism proposed by Thomas et al.,[12] the first step of the reaction is a transmetalation by tin(IV)

(9) For analytical purposes the sequence **7** → **12** was first performed using the pure major isomer **7a**. On the preparative scale we used the mixture of diastereoisomers.

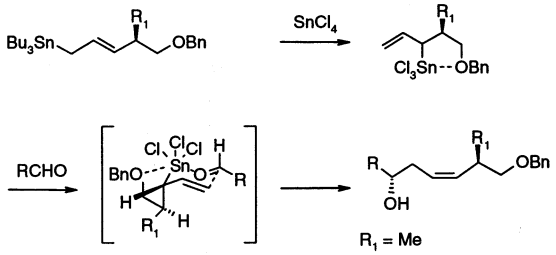
(10) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem*. **1999**, *64*, 663−665.

(11) Smith, A. B., III; Doughty, V.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Yakeudi, M. *Org. Lett*. **2002**, *4*, 783−786.

(12) Carey, J. S.; Coulter, T. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3933−3934 and references therein.

(13) Oha, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1−20.

(14) Weigand, S.; Brückner, R. *Synthesis* **1996**, 475−482 and references therein.



chloride to give an intermediate believed to react via a six-membered transition state. The *Z* configuration is the result of a complexation of $SnCl_3$ by the OBn group, while the stereochemistry of the newly created asymmetric center is imposed solely by the configuration of the carbon atom bearing the R_1 substituent. To the best of our knowledge, no example of this reaction using an unsubstituted allylstannane ($R_1 = H$) has been reported so far. In our case, as might have been expected from Thomas's proposal, the reaction showed an excellent "*Z* preference" but a poor selectivity when considering the newly formed chiral carbon atom, with a slight preference for the "anticram" product 16(*R*) **15**. Deprotection of both the terminal olefinic double bond and OH-6 was cleanly effected by treatment with butyllithium at low temperature (with recovery of some starting material). Finally DDQ removal of the last PMB protecting group afforded Attenol A.

Several features of this synthesis are worth mentioning. In view of earlier findings in our laboratory using similar precursors,[3] the extreme reluctance of silylketal 11(*R*) **9** to ring-cyclize was unexpected.[15] In the present case, no change of solvent or catalyst led to completion of the coupling reaction. Clearly, more methodological studies are needed before one can predict with certainty the outcome of a particular RCM. We were very pleased that our concerns regarding the feasibility of using iodoetherification for simultaneous protection of the hydroxyl and olefinic double bond in a 1,5-ene-ol proved not to be justified. In fact, the method perfectly served its purpose: the iodine could be introduced very early in the synthesis, carried through the almost complete synthetic sequence, and cleanly removed toward the end of the synthesis.

Finally, the present work further shows the potential of silicon tether-aided coupling metathesis for the synthesis of complex spiroketal-containing systems, which was the main purpose of this communication. Obviously, for the method to be competitive from the preparative viewpoint, several steps (in particular the RCM step) will have to be improved. Work along these lines is underway in our laboratory.

Acknowledgment. We thank Drs. Didier Le Nouen and Stéphane Bourg for help with NMR recording and interpretation.

Supporting Information Available: Selected experimental procedures and ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The requirement of adequately substituted precursors for the success of the RCM reaction, in particular in the case of eight-membered ring formation, is known: (a) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643*−*644*; 247−252. (b) Cui, J.; Evans, P. A. *Abstracts of Papers*, 223rd National Meeting of the American Chemical Society, Orlando, FL; American Chemical Society: Washington, DC, 2002; ORGN 276. (c) Our work; see ref 3.