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A General Stereocontrolled, Convergent Synthesis of Oligoprenols That Parallels the Biosynthetic Pathway

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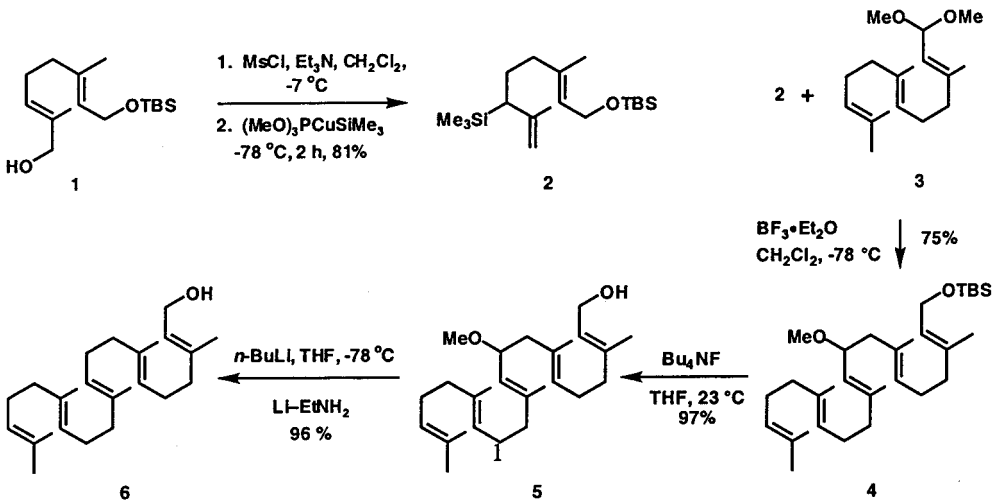
All-*E* oligoprenols, from *E*-geraniol (*E*-diprenol) to *E*-solanesol (all-*E* nonaprenol),[1] are important naturally occurring compounds not only in themselves but also as biosynthetic precursors of many thousands of complex isoprenoids as well as prenylated proteins and carbohydrates.[2] In addition, it has been postulated that oligoprenol phosphates may have been important membrane and cell components in the early development of life.[3] The biosynthesis of oligoprenols occurs by a 5-carbon homologation process (prenylation) in which a prenyl (or oligoprenyl) pyrophosphate derived cation attaches to the terminal olefinic carbon of the 5-carbon species, 4-methyl-3-butenyl pyrophosphate.[4] Despite the apparent simplicity of this coupling process and its appreciation for several decades, a chemical (i.e. nonenzymic) version has not previously been implemented. In fact, the only type of coupling that has been used successfully to date for the synthesis of oligoprenols, e.g. all-*E* geranylgeraniol, is the S_N2 reaction of a phenylthio stabilized allylic lithium reagent with an allylic bromide (Biellmann−Ducep coupling[5]).[6,7] Reported herein is an efficient, convergent, and general route for the synthesis of all-*E* oligoprenols that parallels the biosynthetic process because it is both cationic and highly *E*-stereoselective. The synthesis is strategically powerful since it allows the coupling of two fragments each of which can have multiple prenyl units. Its generality has been demonstrated by the syntheses of all-*E* geranylgeraniol (2+2 coupling), geranylfarnesol (3+2 coupling), farnesylfarnesol (3+3 and 4+2 coupling), and heptaprenol (farnesylgeranylgeraniol, 3+4 coupling). As a specific illustration, we describe the synthesis of all-*E* pentaprenol (geranylfarnesol) by the pathway shown in Scheme 1.

Monoprotected diol **1** (prepared in 40% yield from *E*-geranyl-*tert*-butyldimethylsilyl (TBS) ether by heating with selenium dioxide and pyridine in ethanol at reflux and subsequent reduction of the crude product with $NaBH_4$ in ethanol at 0 °C)[8] was transformed into the corresponding mesylate, as shown. Reaction of this mesylate with the reagent $Me_3SiCuP(OMe)_3$ (prepared from Me_3SiLi and $ICuP(OMe)_3$)[9] in THF−HMPA−Et_2O (9:1:0.75) at −78 °C for 2 h and then at −78 to 20 °C over 1 h afforded exclusively S_N2' displacement product **2** (81% isolated yield from **1**). The isomeric primary TMS derivative (from S_N2 displacement) could not be detected by careful 500 MHz ^1H NMR analysis of the total reaction product. *E*,*E*-Farnesal dimethylacetal (**3**), the reactant required in the crucial coupling step, could not be prepared from *E*,*E*-farnesal using a variety of known procedures, including one recently described,[10] since extensive $E \rightarrow Z$ isomerization invariably occurred. After considerable experimentation it was discovered that pure *E*,*E*-**3** could be prepared from *E*,*E*-farnesal in 97% yield under very carefully controlled conditions in the following way. A mixture of 1:1 CH_2Cl_2−dry MeOH was treated with 2 equiv of $(MeO)_4C$ (based on aldehyde) and 0.9 equiv of $BF_3{\cdot}Et_2O$ at 23 °C for 10 min. The mixture was cooled to −78 °C and the precooled aldehyde was added slowly. After 1 h at −78 °C the reaction mixture was quenched by addition of Et_3N and saturated aqueous $NaHCO_3$ solution. Extractive isolation (pentane, K_2CO_3 as drying agent) gave pure **3**.

A solution of equivalent amounts of allylic silane **2** and acetal **3** in CH_2Cl_2 at −78 °C was treated dropwise with a precooled CH_2Cl_2 solution of 1 equiv of $BF_3{\cdot}Et_2O$. After 2 h at −78 °C the reaction mixture was quenched with 10 equiv of Et_3N followed by saturated aqueous $NaHCO_3$. Extractive isolation (pentane) followed by flash chromatography on silica gel (99:1 hexanes−EtOAc for elution) gave the pure all-*E* coupling product **4** in 75% yield. Desilylation of **4** (Bu_4NF−THF at 23 °C) gave **5** (97%), which was cleanly converted to all-*E* pentaprenol **6** by sequential reaction

Scheme 1



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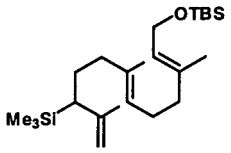
at −78 °C with 1 equiv of *n*-BuLi in THF (to form the lithium alkoxide) and further dropwise addition (titration) of a blue solution of Li in $EtNH_2$ until a faint blue end point was reached. Extractive isolation and flash chromatography on silica gel provided pure (95% by GC analysis) **6** in 96% yield.

All-*E* geranylgeraniol was prepared from *E*-geranial dimethylacetal and silane **2** under the same conditions used for **6** (Scheme 1) (95% purity by GC analysis) with essentially identical yields. Similarly prepared by the method exemplified in Scheme 1 was all-*E* hexaprenol (farnesylfarnesol) from *E*,*E*-farnesal dimethylacetal (**3**) and allylic silane **7**.[11] All-*E* hexaprenol was also made from geranylgeranial dimethylacetal (produced by the method for **3**) and allylic silane **2**. Finally, all-*E* heptaprenol was obtained from **7** and geranylgeranial dimethylacetal by a sequence completely parallel to that outlined in Scheme 1. These results confirm the generality, efficacy, and utility of the new oligoprenol synthesis.



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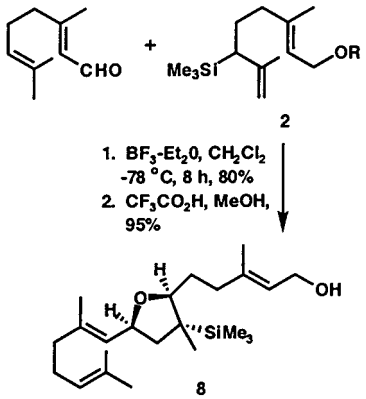
In contrast to the successful synthesis of the series of all-*E* prenols from tetra to hepta members using the acetal coupling method, exemplified by **2** + **3** → **4** in Scheme 1, the use of a free aldehyde for coupling to the allylsilane component **2** or **7** fails due to the intervention of a different reaction pathway. Thus, the reaction of *E*-geranial with **2** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C produces the tetrahydrofuran derivative **8** in good yield. In this case the cationic



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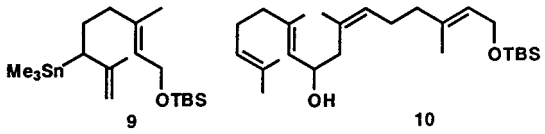
intermediate generated by C−C coupling of the geranial-BF_3 complex and silane **2** undergoes silyl migration and ring closure rather than desilylation. Nor does the use of *E*-geranial, $BF_3{\cdot}Et_2O$, and the trimethyltin substrate **9**[12] (CH_2Cl_2, −78 °C) lead to efficient formation of an oligoprenol derivative. Instead, mixtures of the desired S_E2' and the undesired S_E2 (primary−secondary) coupling products result. Another noteworthy result is the highly stereoselective thermal reaction of *E*-geranial and **9** (neat, 90 °C, 48 h) that produces the *E*,*Z*,*E*-alcohol **10** in 63% isolated yield after flash



9 **10**

chromatography on silica gel. This reaction opens a route for the synthesis of oligoprenols containing a single defined *Z*-olefinic unit, when combined with the selective deoxygenation methodology shown in Scheme 1. The highly selective formation of a new *Z*-olefinic unit in the thermal coupling reaction, which is potentially more widely applicable in the synthesis of isoprenoids, is readily understood in terms of a sterically favored six-membered cyclic transition state of the metalloene type. A full discussion of this thermal *Z*-selective coupling process and its utility in synthesis will be presented elsewhere.

In summary, we have described a remarkably simple solution to the classic unsolved problem of constructing all-*E* oligoprenols by multiprenyl fragment coupling via a cationic pathway analogous to the biosynthetic prenylation process. The success of this process depended not only on the crucial coupling step but also on the development of (1) an efficient synthesis of allylic secondary silanes such as **2** and **7**, (2) stereocontrolled synthesis of *E*-oligoprenal acetals such as **3**, and (3) selective allylic demethoxylation such as **5** → **6**.

Supporting Information Available: Experimental procedures for the compounds described along with NMR, IR, and mass spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Additional steps are required to complete the synthesis of oligoprenols by the Biellmann−Ducep method, the *E*-selectivity of which appears to be approximately 87%.[6a] Yields in the coupling step of 50−75% have been reported.[6]
(8) Fairlamb, I. J. S.; Dickinson, J. M.; Pegg, M. *Tetrahedron Lett.* **2001**, *42*, 2205.
(9) Me_3SiLi was prepared as a red-brown solution by the reaction of $Me_3SiSiMe_3$ in 4:1 THF−HMPA with 1 equiv of MeLi at −7 °C for 15 min; see: Still, W. C. *J. Org. Chem.* **1976**, *41*, 3064. This reagent was added to a solution of $ICuP(OMe)_3$ in THF at −78 °C to give after 15 min the reagent $Me_3SiCuP(OMe)_3$ as a dark-brown solution.
(10) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **1998**, *54*, 15,679. Repeated attempts to prepare **3** by the method described yielded only ca. 1:1 mixtures of *E* and *Z* acetals.
(11) The allylic silane **7** was synthesized from the TBS ether of *E*,*E*-farnesol by an analogous process to that used for **2**.
(12) Substrate **9** was synthesized from the reaction of the mesylate of **1** with $Me_3SnCuP(OMe)_3$.

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