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A SIMPLE SYNTHETIC PROCESS FOR THE ELABORATION OF OLIGOPRENOLS BY STEREOSPECIFIC COUPLING OF DI-, TRI-, OR OLIGOISOPRENOID UNITS

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***Summary**: An effective method of allyl-allyl coupling which is position and stereospecific leads in a simple way to oligoprenols from E-allylic halides.*

Oligoisoprenoids (oligoprenols) play an important role in biochemistry. For example, undecaprenol serves as a carrier of sugars in the biosynthesis of polysaccharides and peptidoglycans;[1] tri- and tetraprenylation of cysteine at the fourth position from the carboxyl terminus is important in Ras proteins, G proteins and viral antigens;[2] oligoprenols are the acyclic precursors of countless cyclic terpenoid natural products.[3] Despite the fundamental importance of this class of compounds and their topological simplicity, no simple, general and practical methods for the synthesis of oligoprenols have been developed, although there has been considerable research in the area.[4] Described herein is a highly effective and broadly useful solution of this problem which relies on the important finding of H. Yamamoto *et al.* that dark red *E*-prenylbarium compounds can be prepared from the corresponding chlorides and Rieke barium.[5]

The new prenylation process can be illustrated by the conversion of geraniol to geranylgeraniol, a valuable intermediate for which there has not been a satisfactory synthesis. The alcohol **1**, readily available from geraniol by silylation with *t*-butyldiphenylsilyl chloride (TBDPSCl) and allylic hydroxylation as described earlier[6] for the corresponding *t*-butyldimethylsilyl ether, was converted to the corresponding bromide **2** (92%) by reaction with 1.2 equiv of methanesulfonyl chloride and 1.3 equiv of triethylamine in CH_2Cl_2 at -40 °C for 1 h and subsequent treatment with 2.5 equiv of lithium bromide in tetrahydrofuran (THF) at 0 °C for 1 h. This bromide was treated with geranylbarium (**3**) (prepared as previously described[5] from 2.5 equiv of geranyl chloride and 2.5 equiv of Rieke barium in THF at -78 °C)[7] in THF solution at -78 °C for 1.6 h and then at 23 °C for 16 h to give, after extractive isolation and column chromatography on C_{18}-silica gel (Millipore Corp. 55-105 μm, elution with CH_3CN), the coupling product **4** (61%). Comparison of **4** with an authentic sample[8] by 400 MHz ^1H NMR, ^{13}C NMR and chromatography demonstrated identity and purity. No geometrical isomers of **4** were detected, indicating that the allyl-allyl coupling is not only specifically primary-primary but also specific with regard to

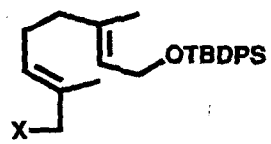
preservation of the *E* geometry of the two allylic units being coupled. Treatment of **4** with 2 equiv of tetra-*n*-butylammonium fluoride in THF at 23 °C for 16 h produced geranylgeraniol (tetraprenol, **5**) which was identical with an authentic sample[8] and pure by ^{1}H NMR and ^{13}C NMR analysis.

Pentaprenol (**8**) was synthesized in a completely analogous manner by the coupling of **2** with the barium reagent **6** from farnesyl chloride[9] which produced the silylated pentaprenol **7** (65%).

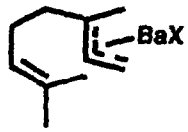
The coupling of the *E,E*-farnesylbarium reagent **6** with farnesyl bromide (**9**)[9] initially at -78 °C (3 h) and then at 23 °C for 16 h afforded, after column chromatography on C_{18}-silica gel (elution initially with CH_3CN, then with isopropyl alcohol to elute the C_{30} product), pure all *E*-squalene (**10**) (79% yield) which was identical with an authentic sample (Fluka Co.) by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral comparison. This process represents the first direct synthesis of all *E*-squalene by the coupling of two *E*, *E*-farnesyl units. This coupling is certain to be useful for the synthesis of analogs of squalene and oxidosqualene, valuable substrates for the study of sterol biosynthesis.

The utility of allylic barium reagents for nucleophilic ring closure was also investigated with interesting results. The epoxy chloride **11**[10] was added to a suspension of Rieke barium in THF and the resulting mixture was stirred for 1 h at -78 °C and 16 h at 23 °C. After extractive workup and column chromatography on silica gel the 14-membered cyclic *E,E,E*-trienol **12** (nephthenol, cembrol A),[11] a natural product of the cembrene family, was obtained in 22% yield along with the C_{40}-diepoxide from head to head coupling of two molecules of **11** (5%) and C_{20}-epoxide from replacement of Cl in **11** by hydrogen (29%). This simple route to cembrol A (**12**) from geraniol also provides ready access to the dehydration product cembrene A[12] and the bicyclic taxol precursor verticillol.[13] It is possible that the yield of cyclization product **12** from epoxy chloride **11** can be improved by accelerating the cyclization step relative to the decomposition of the organobarium reagent. However, preliminary experiments toward this objective (addition of reagents such as baruim or lithium halides, hexamethylphosphorictriamide, or ether) have been negative.

In summary, the results described above demonstrate that prenylic organobarium reagents, for which the term "Yamamoto reagents" seems appropriate, provide an excellent solution to the long standing problems of specific allyl-allyl cross coupling and synthesis of oligoprenols by prenyl extension. The color and stereostability of these reagents are unique and possibly indicate that Yamamoto reagents may have a η^3, π-complex structure which does not rapidly interconvert with the isomeric σ-allylbarium forms.[14,15]



1 X = OH
2 X = Br



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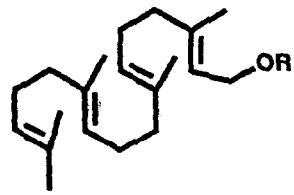
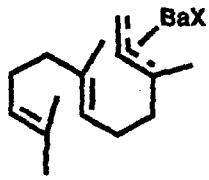
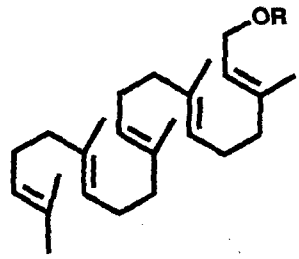


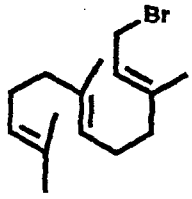
4 R = TBDPS
5 R = H



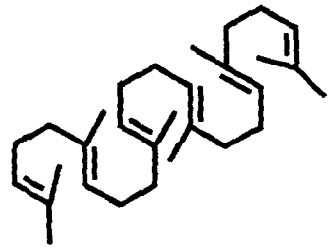
6



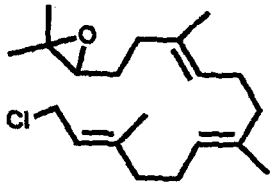
7 R = TBDPS
8 R = H



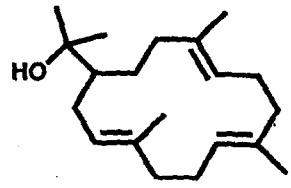
9



10



11



12

TBDPS = *t*-butyldiphenylsilyl

References and Notes

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4. For a summary of existing methods see Cainelli, G.; Cardello, G. *Accts. Chem. Res.* **1981**, *14*, 89-94.
5. Yanagisawa A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893-5895; **1991**, *113*, 8955-8956.
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7. Geranyl and farnesyl barium reagents were obtained as red solutions from the corresponding chlorides in THF using anhydrous barium iodide (made from $BaI_2 \cdot 2H_2O$, Aldrich, 95%) and two equiv of lithium biphenylide as the source of Rieke barium. See Wu, T.-C.; Hiong, H.; Rieke, R.D. *J. Org. Chem.* **1990**, *55*, 5045-5051. We were unable to obtain satisfactory results starting with $BaI_2 \cdot H_2O$ (Fluka, 95%) as the Ba source after drying *in vacuo*, for unknown reasons.
8. Generously provided by the Nissan Flour Co., Japan.
9. *E,E*-Farnesyl chloride was prepared from *E,E*-farnesol (Aldrich Co.) by reaction with 1.2 equiv of methanesulfonyl chloride and 1.3 equiv of triethylamine in CH_2Cl_2 at -40 °C for 30 min, addition of 2 equiv of lithium chloride in THF and stirring at 0 °C for 1 h. Farnesyl bromide was prepared in the same way except for the use of 2 equiv of lithium bromide in THF for the mesylate-halide exchange step.
10. Epoxy chloride **11** was prepared from all *E*-geranylgeraniol by the following sequence: (1) acetylation with Ac_2O-pyridine at 23 °C for 3 h (100%); (2) reaction with 1.1 equiv of *N*-bromosuccinimide in 62:38 THF-H_2O at 0 °C for 1 h to form the distal bromohydrin as major product (62% yield after purification by chromatography on silica gel; (3) treatment with 3 equiv of potassium carbonate in methanol at 23 °C for 2 h to form the epoxy alcohol (98%); and (4) conversion of the epoxy alcohol to the corresponding chloride (**11**) by reaction with 1.2 equiv of methanesulfonyl chloride and 1.4 equiv of triethylamine in CH_2Cl_2 at -40 °C for 30 min and subsequent treatment with 2.5 equiv of lithium chloride in THF at 0 °C for 1 h (96% yield of **11**).
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14. The following procedure for the synthesis of geranylgeraniol is representative.

    To freshly cut lithium metal (7.5 mg, 1.08 mmol) under an argon atmosphere was added a solution of biphenyl (169 mg, 1.1 mmol) in THF (3 mL). The mixture was stirred at room temperature for 2 h forming a greenish-blue solution of lithium biphenylide. To a suspension of anhydrous barium iodide (210 mg, 0.54 mmol, prepared by drying barium iodide dihydrate at 200 °C and 0.05 mm Hg for 1.5 h) in THF (3 mL) was added the preformed lithium biphenylide solution by cannula, and the reaction mixture was stirred at 23 °C for 30 min. To the resulting brown suspension at -78 °C was cannulated a solution of geranyl chloride (93 mg, 0.54 mmol, Aldrich) in THF (1 mL). The reaction mixture was stirred at -78 °C for 30 min to give a red solution of **3**. To the solution of **3** was cannulated a solution of **2** (100 mg, 0.21 mmol) in THF (1 mL) and the reaction mixture was stirred at -78 °C for 1.5 h. The mixture was warmed to room temperature, stirred for 16 h and poured into a mixture of sat. aq. ammonium chloride and ethyl ether. The organic layer was separated, washed with a solution of sat. $Na_2S_2O_3$, and concentrated. The crude product was purified by column chromatography on C_{18}-silica gel (Millipore Corp. preparative C_{18}, 125 Å, 55-105 μm, elution with CH_3CN) to afford **4** (68 mg, 61% yield from **2**) as a colorless oil. To a solution of compound **4** (40 mg, 0.76 mmol) in THF (1 mL) was added n-Bu_4NF (0.15 mL, 1M in THF, 0.15 mmol), and the reaction mixture was stirred at 23 °C for 16 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane-ethyl acetate, 49:1, 19:1, and 5:1) to afford geranylgeraniol (**5**) (21 mg, 95%) as a colorless oil.

15. This research was generously supported by the CIBA-GEIGY Corp. and the National Science Foundation.

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