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CYCLIZATION OF TERPENE ALCOHOLS AND RELATED POLYENOLS BY BENZENESELENENYL TRIFLATE

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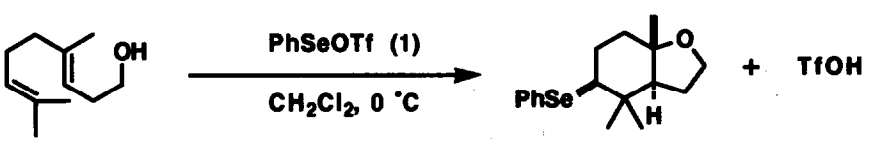
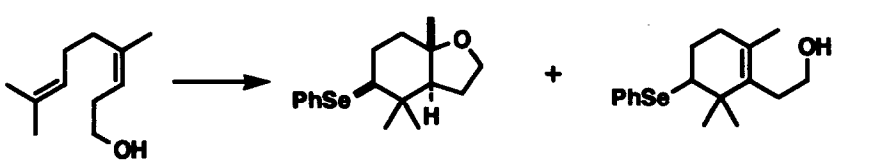
Summary: Electrophilic cyclization of dienols and trienols, such as homogeraniol, homonerol, and farnesol, by benzeneselenenyl triflate proceeds with carbon-carbon bond formation to afford mono-, di-, and tricyclic compounds.

Biomimetic cyclization of terpenoids and related polyenols is an important stereo controlled procedure of polycyclic system[2], and usual organoselenium reagents, for example benzeneselenenyl chloride and *N*-phenylselenophthalimide have been employed as effective C=C bond activating agents in this field.[3] However, these reagents require subsequent strong acidic conditions to accomplish the cyclization of polyenols to give multi-cycles.[4] Described herein is one-step cyclization of acyclic terpene alcohols and derivatives by benzeneselenenyl triflate (PhSeOTf, **1**).[5]

Reaction of homogeraniol (**2**) with one equivalent of **1** in dichloromethane at 0 °C (condition A) gave bicyclic ether **3** (49% yield) as an exclusive product. Homonerol (**4**) reacted with **1** in the same condition to afford **3** and monocyclic alcohol **5** in 42% and 12% yields, respectively. Their homologues **6** and **9** were similarly cyclized in the condition A to give mixtures of bi- and monocyclic products **7** and **8**. In these cases, formation of cis fused products was not detected. Cyclization of *E,E*-farnesol (**10**) and its homologue **12** in



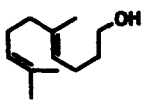
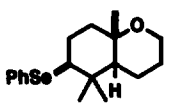
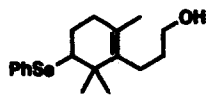
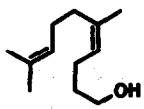
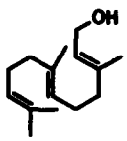
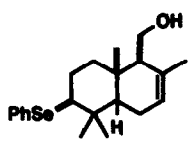
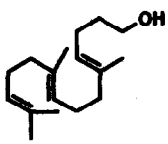
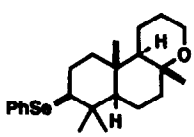
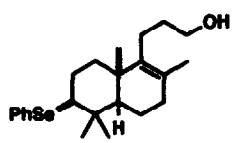
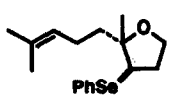
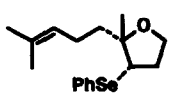
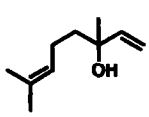
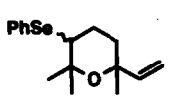
2 **3**



4 **3** **5**

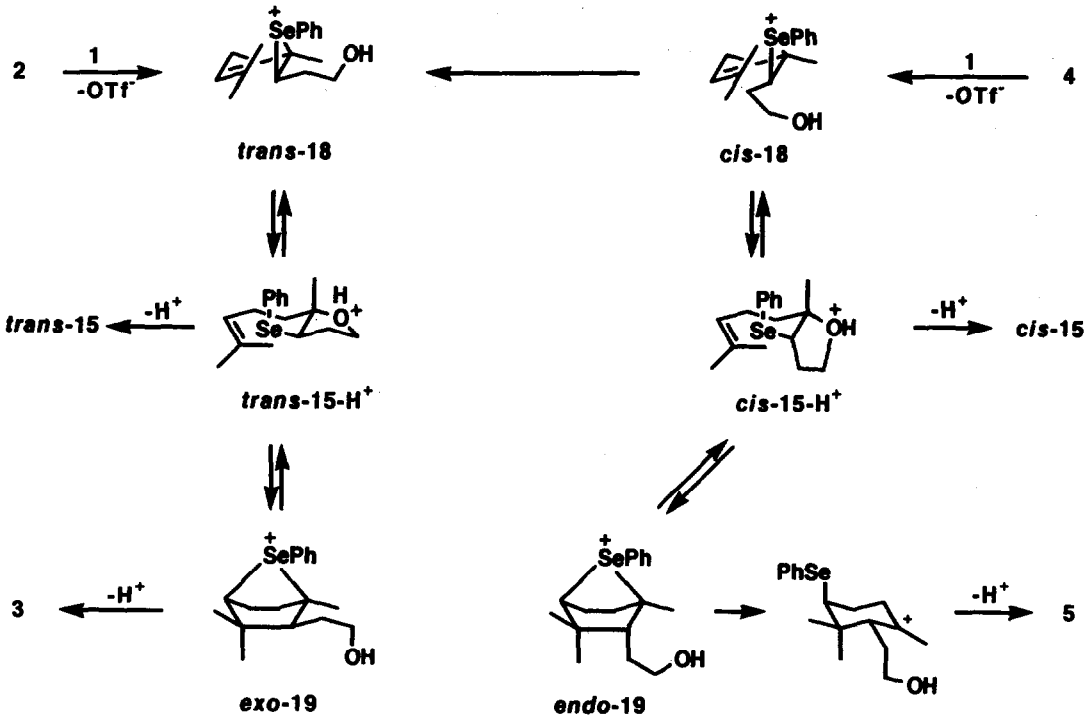
Tf = CF_3SO_2

Table I. Cyclization of Polyenols by Benzeneselenenyl Triflate (1)

substrate	condition	product (yield/%)		
2	**A**	**3** (49)		
4	**A**	**3** (42)	**5** (12)	
 **6**	**A**	 **7**	(30)	 **8** (29)
 **9**	**A**	**7** (17)	**8** (21)	
 **10**	**A**	 **11**	(9)	
 **12**	**A**	 **13**	(7)	 **14** (25)
2	**B**	 ***trans*-15**	(44)	
4	**B**	 ***cis*-15**	(30)	***trans*-15** (6)
4	**C**	***cis*-15** (33)		***trans*-15** (5)
 **16**	**B**	 **17**	(36)	

the condition A proceeded in low yields to give **11** and a mixture of **13** and **14**, respectively. However, geraniol, nerol, linalool, and nerolidol did not give corresponding cyclized products in the condition A. Cyclization of **2** and **4** by **1** in dichloromethane at 0 °C in the presence of equimolar amount of pyridine (condition B) or in dichloromethane at -78 °C (condition C) gave stereoselectively *trans*- and *cis*-**15**, which were formed by the usual intramolecular oxyselenylation process,[4f,4g,4i,5] respectively. Linalool (**16**) gave the oxyselenylation product **17** without carbon-carbon bond formation in the condition B. Results are summarized in Table I.

Electrophilic cyclization of **2** by an organoselenium reagent proceeds through intermediates *trans*-**18** and protonated *trans*-**15** (*trans*-**15**-H^+) to afford *trans*-**15**, which are not changed furthermore in the condition B or C. Under reinforced condition A acid catalyzed second cyclization of *trans*-**15** to **3** carries out through the bicyclic intermediate *exo*-**19**, since the condition A liberates one equivalent of trifluoromethanesulfonic acid throughout the reaction.[6] Related strong acid catalyzed cyclizations were reported.[4f,4g,4i] When the *Z*-isomer **4** was employed to these reaction, the initially produced intermediate *cis*-**18** was converted to sterically unfavorable *endo*-**19**. Here, C-Se bond cleavage of *endo*-**19** occurred predominantly to give a tertiary carbocation intermediate which was transformable to **5** by deprotonation. Some part of *cis*-**18** was isomerized to the more stable *trans*-**18** and yielded **3**. Under the condition B, since deprotonation of *trans*- and *cis*-**15**-H^+ proceeds immediately by pyridine, these intermediates were quenched to give oxyselenylation products *trans*- and *cis*-**15**, respectively.



Following examples are representative. Condition A: To a solution of **1** (1.5 mmol), prepared *in situ* from PhSeCl (287 mg) and AgOTf (386 mg),[7] in CH_2Cl_2 (7 ml) was added a solution of **2** (246 mg, 1.5 mmol) in CH_2Cl_2 (2 ml) at 0 °C. After 15 min, 5% aqNaHCO3 was added and this was extracted 3 times by CH_2Cl_2 (25 ml). The combined organic solution was dried over anhydrous K_2CO_3 and concentrated *in vacuo*. Column chromatography on silica gel eluting with 5% ethyl acetate in petroleum ether gave **3** (230 mg, 49% yield) as colorless oil. Condition B: To a mixture of **1** (1.5 mmol) and pyridine (0.12 ml) in CH_2Cl_2 (7 ml) was added **2** (236 mg, 1.4 mmol) at 0 °C. Similar work-up and purification gave *trans*-**15** (200 mg, 44%) as colorless oil.

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