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Superacidic Cyclization of Bicyclogeranylfarnesic and Geranylfarnesic Acids and their Esters

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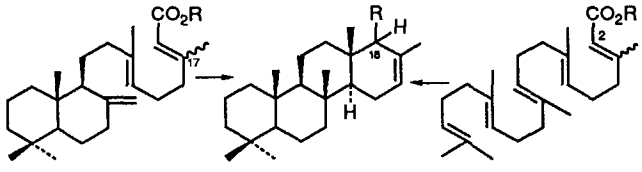
An effective structure-selective stereospecific synthesis of tetracyclic scalarane esters **6** and **7** from bicyclic **2–5** and aliphatic **8–11** precursors has been accomplished.

Scalarane sesterterpenoids having carbon skeleton **1** are exclusively marine organism metabolites. Among these are compounds with interesting biological activity, but they remain rather inaccessible.[1] The few described syntheses of scalaranoids are multi-step and are not very effective.[2–6] However, recently we[7,8] have found that scalarane compounds may be obtained in moderate yield (55–58%) by superacidic cyclization of bicyclic and aliphatic geranylfarnesols and their acetates. Since it is well known that terpenic alcohols and their acetates are labile in acidic media we undertook the investigation of superacidic cyclization of bicyclic and acyclic sesterterpenic acids and their esters, taking into consideration the fact that carboxylic and ester functional groups are more stable. The results of this investigation are the subject of this Communication.

In order to obtain optically active scalaranes we carried out

the fluorosulfonic acid cyclization of stereoisomeric esters **2** and **3** and the respective acids **4** and **5** which have been prepared according to ref. 2 from manool. It should be noted that the electrophilic cyclization of esters **2** and **3** has already been studied by Herz and Prasad,[2] who used stannic chloride as the cyclization reagent. However, the reaction turned out to be structurally unselective, complex mixtures of compounds were formed and consequently the isolation of the target products involved certain experimental difficulties.

The superacidic cyclization of the methyl ester of 17*E*-bicyclogeranylgeranic acid **2** in 2-nitropropane (20 mol equiv. FSO_3H, − 50 °C, 30 min) gave a sole product – the known tetracyclic ester **6**[2] [m.p. 167–169 °C (from petroleum ether), $[\alpha]_D^{22}$ + 65.9° (*c* 3.6, $CHCl_3$), yield 82%}, which was easily isolated by column chromatography on silica gel.



2; R = Me, 17*E*
3; R = Me, 17*Z*
4; R = H, 17*E*
5; R = H, 17*Z*

1; R = Me, dihydro
6; R = CO_2Me, 18α-*H*
7; R = CO_2Me, 18β-*H*

8; R = H, 2*E*
9; R = H, 2*Z*
10; R = Me, 2*E*
11; R = Me, 2*Z*

On cyclization under the same conditions the stereoisomeric bicyclic 17*Z*-ester **3** afforded the epimeric tetracyclic ester **7** {viscous oil, $[\alpha]_D^{25}$ − 26.5° (*c* 2.3, $CHCl_3$), yield 78%}. Compounds **6** and **7** were identified by comparing their physicochemical and spectroscopic characteristics with published data.[2]

The cyclization of stereoisomeric 17*E*- and 17*Z*-bicyclogeranylfarnesic acids **4** and **5** needs more vigorous conditions than their esters **2** and **3**. Indeed the cyclization of 17*E*-acid **4** proceeded at − 45 °C within 30 min. After diazomethane methylation of the reaction product, ester **6** was isolated in 80% yield. Under the same conditions 17*Z*-acid **5** led to the epimeric ester **7** in 74% yield.

Thus, the fluorosulfonic acid cyclization of stereoisomeric bicyclogeranylfarnesic acids and their esters represents a highly effective structurally selective, chemo- and stereo-selective route to tetracyclic optically active scalarane sesterterpenoids which, for the first time, were prepared in one step in 80% yield.

The excellent results obtained on superacidic cyclization of bicyclic sesterterpenoids to tetracyclic scalarane ones prompted us to use this method for elaboration of a biomimetic synthesis of the latter directly from aliphatic precursors.

The starting compounds **8–11** were synthesized according to ref. 8 from *E,E*-geranyllinalool. The fluorosulfonic acid treatment of *E,E,E,E*-geranylfarnesic acid **8** (25 mol equiv. FSO_3H, − 40 °C, 50 min) in 2-nitropropane with subsequent methylation of the reaction product by diazomethane resulted in a 70% yield of racemic ester **6** which was identified by chromatographic and spectroscopic comparison with its optically active sample. Under the same conditions, but within 1.5 h, the *Z,E,E,E*-geranylfarnesic acid **9** gave epimeric racemic ester **7** (67% yield). The cyclization of esters **10** and **11** of acids **8** and **9** proceeds under milder conditions. Thus, *trans*-ester **10** was converted into tetracyclic ester **6** at − 45 °C (25 mol equiv. FSO_3H, 50 min, yield 72%). Under similar conditions (− 40 °C, 1 h) *cis*-ester **11** afforded (±)-scalarane **7** in 70% yield.

It should be noted that the product yields obtained for the cyclization of *cis*-compounds are lower than those for the respective *trans*-isomers.

The only byproduct of the superacidic cyclization reaction is a polymeric one which can be easily separated by chromatography. The amount of the polymeric product formed was higher for the cyclization of aliphatic than of bicyclic sesterterpenoids and for *cis*- than of *trans*-isomers.

Hence, we have succeeded in achieving, for the first time, the one-step biomimetic structurally selective, chemo- and stereospecific conversion of pentaenic acyclic sesterterpenoids into tetracyclic scalarane compounds containing seven asymmetric centres.

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