Tetrahedron Letters, Vol. 33, No. 13, pp. 1679-1682, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

POLYENE CYCLIZATIONS USING MERCURY (II) TRIFLATE - N,N-DIMETHYLANILINE COMPLEX - PARTICIPATION BY INTERNAL NUCLEOPHILES

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Key Words: Polyene cyclizations; mercuric ion; internal nucleophilic termination

Abstract

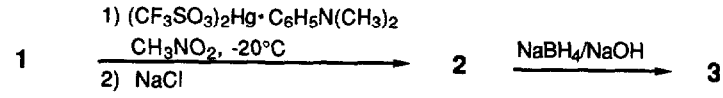
The cyclization of a number of functionalized polyenes with mercuric triflate - N,N-dimethylaniline complex (Nishizawa's reagent) to give bicyclic or tricyclic products has been studied. Suitably positioned internal nucleophiles, such as carbonyl, hydroxy and β-ketoester groups were found to participate to varying extent, in the termination of these cyclizations.

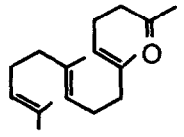
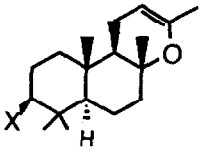
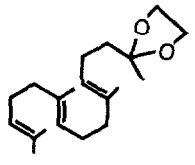
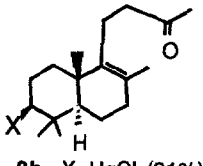
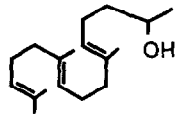
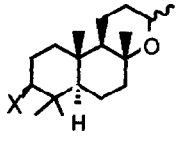
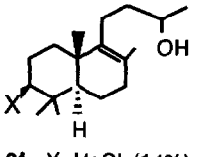
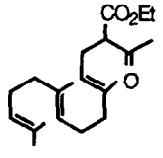
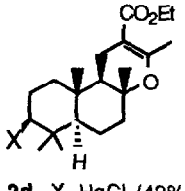
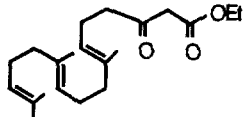
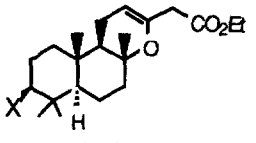
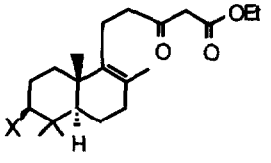
Cyclization of polyene substrates with a variety of electrophiles including protons, bromonium ions, Lewis acids,[1,2] sulfenium ions,[3] benzeneselenyl triflate[3] and mercuric ions[4-9] is an important biomimetic route for the synthesis of polycyclic terpenoids. Some time ago, Nishizawa and coworkers reported on the preparation of a new reagent, mercury (II) triflate-N,N-dimethylaniline complex, and its applications to polyene cyclizations.[4] They found this reagent gave greater selectivity and better yields in the cyclization of various farnesol derivatives in comparison with other mercuric salts for example mercury (II) trifluoroacetate. The mechanistic aspects of this cyclization and applications to the synthesis of some diterpenoids have been examined by the same group.[5,6]

We were interested in examining the application of Nishizawa's reagent for the cyclization of a number of functionalized polyene substrates. Of particular interest to us was the ability of various oxygen containing functional groups to serve as internal nucleophiles in the termination of these cyclizations. This could provide a method for the preparation of functionalized tricyclic compounds, potential intermediates in diterpenoid synthesis. Hoye and others[7,8] have examined such internal nucleophilic termination in mercury (II) trifluoroacetate cyclization of dienes leading to bicyclic products. An advantage in these reactions in comparison to those carried out with Lewis acids is the fact that cyclization occurs exclusively on oxygen rather than carbon in the case of suitably positioned β-ketoesters. In examples of tricyclic ring formation using mercuric ion studied so far, either alkenes,[6a] furans[6b] or enol phosphates[9] have served as terminators, and cyclization occurs only on carbon, leading to carbocycles.

All the polyenes required for our studies were prepared from commercially available *trans, trans* farnesol (Aldrich Chemical Co.) via its chloride by known procedures.[10] *trans, trans* Farnesyl acetone (**1a**) was protected (ethylene glycol, PPTS, benzene) to give the ketal **1b** or reduced to the alcohol **1c** with sodium borohydride in ethanol. Substrates **1d** and **1e** were synthesized by alkylation of farnesyl chloride with the sodium salt of ethyl acetoacetate or the corresponding dianion respectively. Both the preparation of the mercury reagent and the cyclization protocol used were similar to those already reported.[4-6] Cyclization was effected with mercury (II) triflate - N,N-dimethylaniline complex at -20°C to -15°C in nitromethane and the reaction mixture subsequently treated with aqueous sodium chloride. The organomercury products **2** from the cyclization reactions were isolated

Table 1. Cyclization of Farnesol Derivatives



entry	substrate	products (yield)	
1	 **1a**	 **2a** X=HgCl (39%) **3a** X=H (58%)	
2	 **1b**	 **2b** X=HgCl (31%) **3b** X=H (35%) + **3f** X=H (28%)	
3	 **1c**	 **2c** X=HgCl (15%) **3c** X=H (33%)	 **2f** X=HgCl (14%) **3f** X=H (34%)
4	 **1d**	 **2d** X=HgCl (43%) **3d** X=H (76%)	
5	 **1e**	 **2e** X=HgCl (55%) **3e** X=H (47%)	 **2g** X=HgCl (8%)

by careful column chromatography. Subsequent reductive demercuration with $NaBH_4$/NaOH gave **3**, which were more suited for complete characterization.

The cyclization of farnesylacetone[11] (**1a**) to the tricyclic enol ether **2a** proceeds in moderate yields. Demercuration of **2a** yields sclareoloxide **3a**, a well known synthetic intermediate.[12,13] In contrast, the corresponding ketal **1b** gave the tetrasubstituted bicyclic ketone **2b** as the major product upon work up, along with varying amounts of the corresponding ketal, and small amounts of the trisubstituted alkene. Thus, the cyclization can be controlled to give either the bicyclic or tricyclic products by protection of the carbonyl group of **1a**. Reduction of the ketone **2b** with alkaline $NaBH_4$ gave a mixture of the demercurated ketone **3b** and the alcohol **3f** which were readily separated. The conversion of the ketone **3b** to d,l-ambreinolide has already been reported.[14]

The cyclization of the alcohol **1c** resulted in the formation of both tricyclic and bicyclic products in about equal amounts. Demercuration of **2c** gave the cyclic ether **3c** as a mixture of stereoisomers. These compounds are homologs of ambrox® and of interest due to their potential ambergris like odors.[15] The β-ketoesters **1d** and **1e** gave the tricyclic products **2d** and **2e**, respectively, arising from participation of their carbonyl oxygens, as the major products in synthetically useful yields.[16,17] The formation of the endocyclic enol ethers in both these cases is worthy of note.

In contrast to the tricyclic products, the bicyclic products obtained from our studies were often contaminated with small amounts of the Δ 7,8 trisubstituted alkene isomers even after purification. In these cases the separation of the minor isomers from the major product was difficult to achieve by column chromatography. It is interesting to note that while cyclization of some farnesol derivatives leads to predominantly the trisubstitued Δ 7,8 alkene,[4] in other cases including our examples, the major products formed are the tetrasubstituted Δ 8,9 alkenes. The reason for the difference in selectivity in the elimination at the terminal carbocationic site in these cyclizations is not clear.

In conclusion, it has been shown that internal oxygen nucleophiles can be successfully used as terminators in cyclizations involving Nishizawa's reagent. A variety of functionalized tricyclic intermediates have been prepared that have potential applications to diterpenoid synthesis. This reaction can be used for the preparation of both bicyclic and tricyclic products by variation of functionalities in the polyene precursors.

Acknowledgement

The NIH MARC Program (Fellowship to R.P.) and the Crimson Scholar Programs (NMSU) are thanked for their support of this research. Also we would like to acknowledge NSF (Grant No. 8814575) for funds to obtain a high field NMR.

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13. The structure of **3a** was confirmed by comparisons with an authentic sample kindly furnished by Dr. Ferdinand Naf, Firmenich SA, Geneva, Switzerland. Both Dr. Naf and Dr. R.C. Cambie, University of Auckland, New Zealand are thanked for their assistance in this matter. The vinyl ether **3a** is an unstable compound, as noted previously in the literature.
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16. The stereochemical assignments of the products are based on the well established precedence in such cyclizations and spectral comparisons with known intermediates where applicable. For a detailed discussion of the mechanistic implications of the cyclization process see Ref. 2. Spectral data (^{1}H NMR, ^{13}C NMR, IR, mass spectra) were consistent with assigned structures.
17. The product **2e** was contaminated with small amounts of the bicyclic product. Further purification and characterization was readily achieved after reduction to **3e**.

(Received in USA 26 November 1991)