

SYNTHESIS OF AN ISOMER OF THE GERMACRANOLIDE ISOARISTOLACTONE

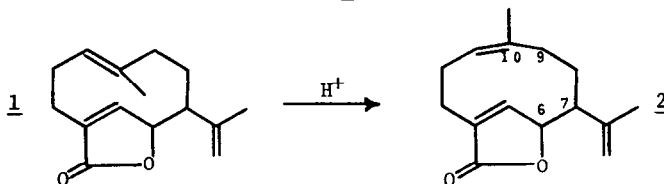
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Abstract: Photocycloaddition of (+)-isopiperitenone and cyclobutene-1-carboxylic acid gives an adduct which upon reduction with NaCNBH₃ followed by thermolysis yields an isomer of isoaristolactone in an overall yield of 26%.

Aristolactone (1), a germacranolide isolated from *Aristolochia serpentaria* and *A. reticulata*, yields isoaristolactone (2) upon treatment with dilute acid.^{1,2} In the structural elucidation of these compounds the relative configuration of the substituents at C₆ and C₇ was not determined¹ but in the great majority of germacranolides these substituents are in a *trans* orientation.³ We chose as an initial synthetic target lactone 2 in which these groups were *trans*.



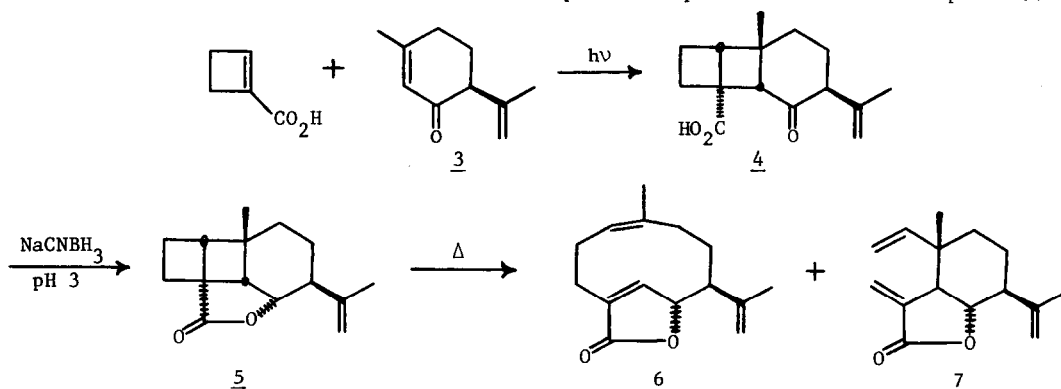
Our approach to the synthesis of one of the possible isomers of 2 employed a photoaddition-thermolysis sequence which has been used by us⁴ and others⁵ for the generation of medium ring systems. Irradiation of (+)-isopiperitenone (3)⁶ and a four-fold excess of cyclobutene-1-carboxylic acid in benzene with a 350-nm source gave adduct 4,⁷ mp 126-127°. Reduction of the acid 4 with NaCNBH₃ at pH 3⁸ afforded lactone 5: mp 139-140°; [α]_D²² -17.5°; ir (CCl₄) 3090, 1765, 1645, 1200, 895 cm⁻¹; nmr (CCl₄) δ 1.25 (3H, s), 1.79 (3H, s), 1.5-2.9 (11H, m), 4.5-5.0 (3H, m).

The overall yield for the conversion of reacted 3 to lactone 5 was 40%. A four-fold excess of cyclobutenecarboxylic acid was needed to minimize the intramolecular photoaddition of 3⁹ but nevertheless almost 20% reacted by this route. The use of *acid 4*¹⁰ and NaCNBH₃ in the reduction step offered a considerable improvement over related reductions,^{4b,5c} in which the keto *ester* and NaBH₄ were used.¹¹ The overall yield stated was obtained without purification of acid 4 (obtained by bicarbonate extraction of the irradiation mixture) and essentially the only product in the neutral fraction after the reduction was the desired lactone 5.

Thermolysis of 5 in refluxing decane (174°) for 3.5 hrs. afforded 64% of the isoaristolactone isomer 6 and 14% of the Cope rearrangement product 7. A comparison of the data for 6 with that reported^{1,2} for isoaristolactone (shown in parentheses) clearly indicates these are different compounds: an oil (mp 90°); [α]_D²² +264° (-44°); ir (CCl₄) 3080, 3015, 1765, 1645, 1190, 895 cm⁻¹ (1765, 1655, 892); nmr (CCl₄) 1.60 (3H, s), 1.85 (3H, s), 1.5-2.5 (8H, m), 2.84 (1H, m), 4.85

(1H, s), 5.00 (1H, s), 5.20 (1H, m), 5.40 (1H, d, $J=4.2$ Hz), 7.34 (1H, s) [1.59 (3H, s), 1.86 (3H, s), 6.8 (1H)]; uv λ_{\max} (EtOH) 217 nm (ϵ 10,000) [209 nm (11,200)]. Thus we assume either the orientation of the C_6 and C_7 substituents is opposite in the two compounds or in the acid-catalyzed isomerization of 1 the C_1 - C_{10} double bond migrates to the C_9 - C_{10} position. We have recently obtained a source of aristolactone (Virginia snake root) and consequently comparisons of synthetic and natural products in this series will be greatly facilitated.

In conclusion, we have reported a convergent three-step synthesis of the germacranolide 6 in an overall yield of 26% and have shown that this product differs in structure from isoaristolactone derived from naturally occurring aristolactone. Optically active complex molecules such as 6, which are now readily available by the approach outlined, may serve as useful substrates for a variety of different reactions as well as potential precursors of natural products.¹²



References and Notes

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- All new compounds gave spectral and analytical data consistent with their structures.
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- We thank Professor R.A. Raphael, Cambridge University, for suggesting the use of the acid rather than the ester in these reductions.
- The overall yield in the previously reported^{4b} sequence of piperitone \rightarrow dihydro 5 has been improved from 26% to over 60% using this new reduction procedure.
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