Pergamon

Tetrahedron Letters 40 (1999) 6339–6342

TETRAHEDRON LETTERS

First enantioselective total synthesis of the endogenous natriuretic agent LLU-α

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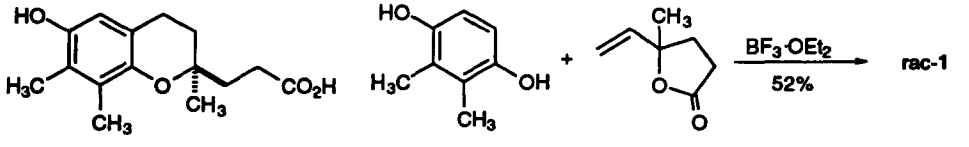
Received 27 May 1999; accepted 15 June 1999

Abstract

The endogenous natriuretic agent LLU-α, **1**, has been synthesized from geraniol **4** in 13 steps and 18% overall yield. The two key steps are a Gassman–Sato process to give the phenol **8** and cyclization of the triol **10** with acid to give the chroman **12** with retention of configuration at the tertiary alcohol center. Final oxidation gave **1**.

Several years ago we reported the isolation of the endogenous diuretic agent LLU-α,[1] which was both natriuretic and eukaluretic. The structure of this compound was determined by spectroscopic analysis to be **1**, a presumed metabolite of γ-tocopherol.[2] The structure was proven by a racemic synthesis from the commercially available 2,3-dimethylhydroquinone **2** and the readily available lactone **3**, which afforded racemic **1** in good yield.[2] The absolute stereochemistry was determined by X-ray crystal structure determination of the amide formed from **1** and an optically pure amine.[3] Although enantiopure **1** could be separated from its enantiomer by chiral HPLC, this was not suitable for the preparation of large quantities of optically pure **1** or its analogues. We report herein the first enantioselective total synthesis of LLU-α **1** from readily available starting materials.



The synthesis (Scheme 1) begins with the Sharpless asymmetric epoxidation[4] of commercially available geraniol **4** giving the expected epoxy alcohol in 91% yield.[5] The optical purity of this alcohol was shown to be 94% by ^{31}P NMR spectroscopy of the diastereomeric phosphorous derivative by the method of Alexakis.[6] Hydride reduction gave the desired 1,3-diol **5** in 99% yield.[5] Tosylation of the primary alcohol and displacement with the sodium salt of isopropyl mercaptan followed by acetylation

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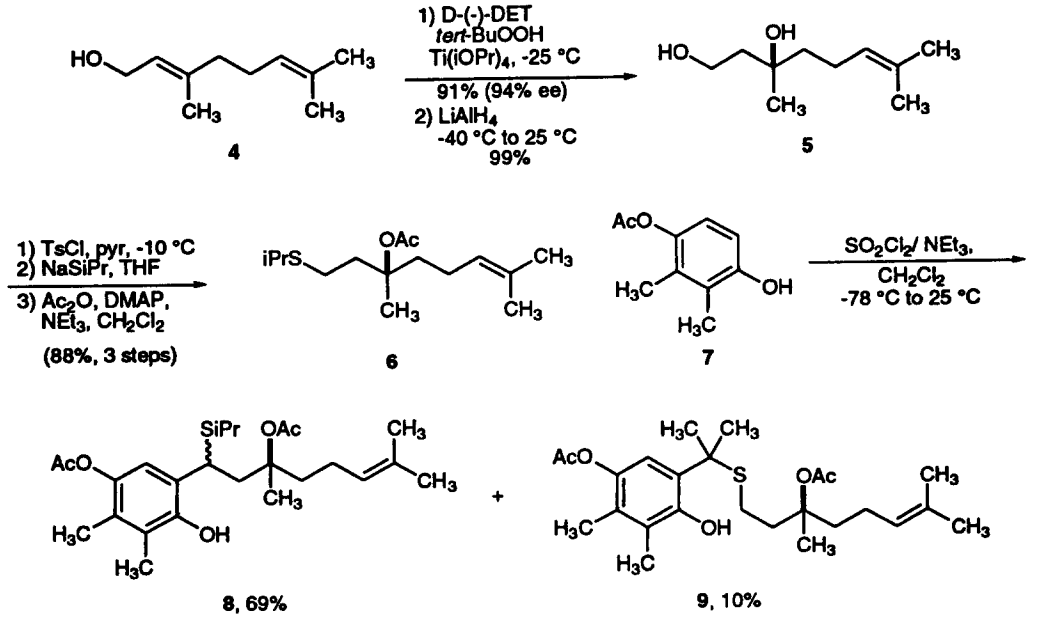
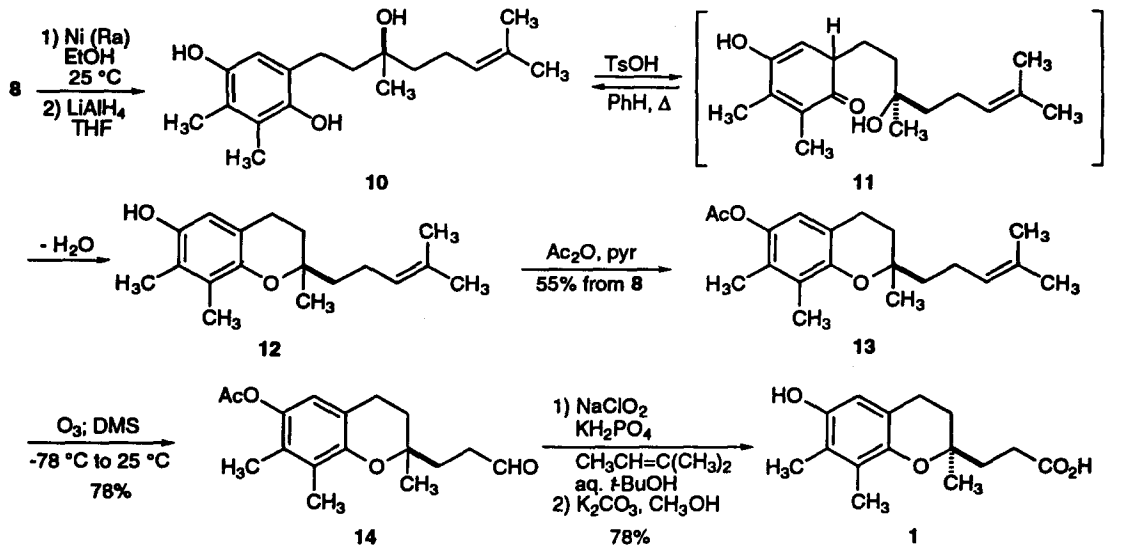
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01204-6

of the tertiary alcohol gave the isopropylthio acetate **6** in 88% overall yield. One of the two key steps of this synthesis involves the application of the chemistry developed by Gassman,[7] namely reaction of the chlorosulfonium salt prepared from the sulfide **6** and sulfuryl chloride in the presence of the hydroquinone monoacetate **7** (made by acetylation of the commercially available hydroquinone). This afforded a separable mixture of two products, the desired isopropylthio phenol **8** in 69% yield along with the product of activation of the other α-carbon, namely the phenol **9** which was formed in 10% yield. Thus the desired phenol **8** is available as a 1:1 mixture of diastereomers at the benzylic carbon in 55% yield from geraniol **4** by chemistry that is easily scaled.



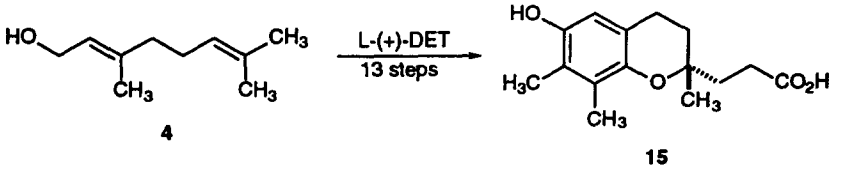
Scheme 1.

The completion of the synthesis (Scheme 2) involves reductive desulfurization with Raney nickel followed by hydride reduction to remove both acetates to generate the hydroquinone alcohol **10**. The second key step of the synthesis is the acid-catalyzed cyclization to afford the dihydrobenzopyran (chroman) ring system. A solution of **10** in benzene was heated at reflux with a catalytic amount of *p*-toluenesulfonic acid to produce the chroman **12** with mostly retention of configuration at the tertiary alcohol center. Acetylation then furnished the desired chroman **13** in 55% overall yield from the sulfide **8**.[8] One possible mechanism consistent with the observed stereoselectivity involves protonation of the electron-rich aromatic ring to cause the reversible formation of the cyclohexadienone **11**[9] (and its protonated forms) which is then attacked intramolecularly by the tertiary hydroxyl group to give an intermediate which then loses water to generate the chroman **12**.[10] The stereochemistry of this reaction was shown to be mainly retention of configuration by comparison of the LLU-α **1** prepared by this route with the natural material (the racemic synthetic material prepared earlier[2] could be separated into the two enantiomers by chiral HPLC).[11] The synthesis of LLU-α was completed in three steps: first, ozonolysis of the trisubstituted alkene to give, after reductive workup, the aldehyde **14**, and then sodium chlorite oxidation[12] to the acid and finally basic hydrolysis of the phenolic acetate to afford LLU-α **1** in 61% yield for the three steps. The LLU-α **1** was shown to be >95% the *S* enantiomer (90.5% ee),[13] which implies that the key cyclization reaction was approximately 96% stereoselective. Thus, optically active LLU-α **1** is available from geraniol **4** in 13 steps and 18% overall yield.



Scheme 2.

We have also prepared the enantiomer of LLU-α, **15**, by exactly the same sequence but using the opposite tartrate in the initial Sharpless epoxidation of geraniol **4**. Again chiral HPLC was used to demonstrate its identity with the unnatural LLU-α. We have also used nerol[14] rather than geraniol in the asymmetric epoxidation but the enantiomeric excess of the intermediate **5** that we obtained was poorer. Further work on the use of this chemistry and others to produce analogues of LLU-α is currently under way in our laboratories.



Acknowledgements

We thank the National Institutes of Health (HL 56066) for generous financial support.

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6. The optical purity of this epoxy alcohol was determined by ^{31}P NMR of the diastereomeric phosphorodiamidites formed by reaction of the alcohol with *R,R*-octahydro-*N,N*-1,3-tetramethyl-1,3,2-benzodiazaphosphol-2-amine by the method of Alexakis: Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437.
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9. We do not have any chemical evidence for the existence of this cyclohexadienone **11** but only postulate that it may be an intermediate based on the earlier work of Cohen.[10b]
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11. Chiral high-pressure liquid chromatography was run on a Beckman Gold System on an (*S,S*) Whelk-O 1 column (Regis Chemical) with 85:15:0.5, hexane:isopropanol:acetic acid as the solvent and a flow rate of 1 mL/min with UV monitoring at 295 nm. We thank Drs. Dave Murray, Oleg Aleksiuk, Elaine Benaksas, and Karina Gibson and Katrina Wendt at Loma Linda University for the chiral HPLC experiments.
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13. Reduction of the aldehyde **14** with lithium tri(*tert*-butoxy)aluminum hydride gave the corresponding primary alcohol (with the phenyl acetate still intact) in 90% yield. Analysis of this alcohol by the method of Alexakis described above[6] indicated an isomeric purity of 90.5% ee. The major product was shown to be the desired *S* enantiomer by chiral HPLC as described above.[11]
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