Tetrahedron Letters, Vol 33, No 4 pp 437-440 1992
Printed in Great Britain

0040 4039/92 $3 00 + 00
Pergamon Press plc

SYNTHESIS AND ABSOLUTE CONFIGURATION OF POLYPROPIONATE METABOLITES OF *SIPHONARIA AUSTRALIS*

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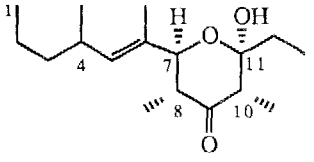
Summary An enantioselective synthesis of a C_{17} metabolite from *Siphonaria australis* has been accomplished This has led to the assignment of the absolute configuration of two metabolites in this series through the use of the exciton chirality method

The metabolite 1 and its degradative partner 2 were isolated from *Siphonaria australis*, an air-breathing mollusc obtained along the coast of Auckland, New Zealand by Faulkner and co-workers [1] Metabolite 1 is one of the simplest cases of hemiacetal-containing polypropionates in the *Siphonaria* series [2] It is reasonable that 1 exists in the lowest energy conformation of all of its possible ring stereoisomers, one in which the alkyl groups are in an equatorial orientation The hydroxyl group is axial, presumably due to the maximization of a ground state anomeric effect



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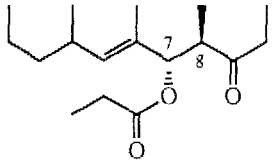


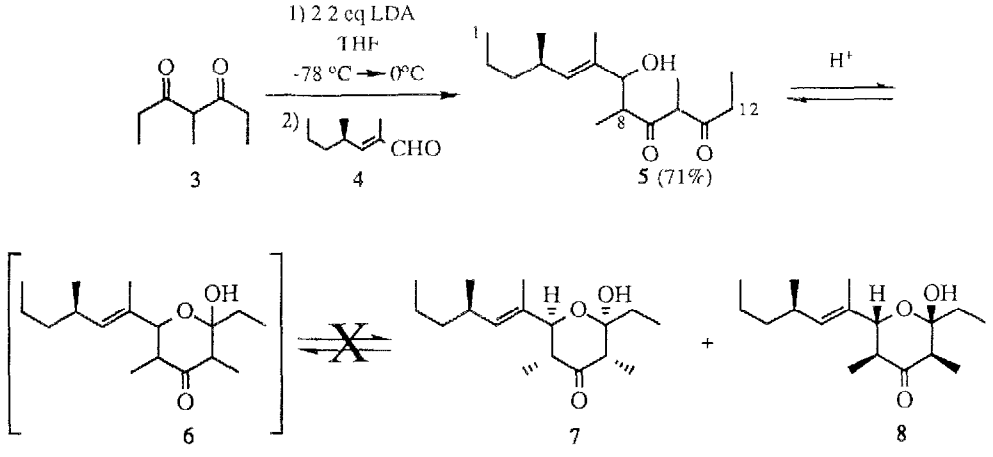
2

Currently, the synthetic methods used in setting relative stereocenters in acyclic polypropionates are kinetically based [3] Our original strategy toward the synthesis of 1 involved the use of thermodynamic multiple equilibration methods to establish the relative stereochemistry in the hemiacetal ring Through this process, it should be possible to use the absolute stereochemistry of C7 to control the other three stereogenic centers in the ring An additional complication in this synthesis is that the stereochemistry of C4 and the absolute stereochemistry of the natural product were unknown Herein, we disclose our work in this area which has culminated in the synthesis of 2 and the determination of the full structures and absolute stereochemistry of 1 and 2

We began our investigations with the aldol condensation of 4-methyl-3,5-heptanedione (3)[4] with the known chiral aldehyde 4[5] (Scheme I) The resulting adduct 5 (overall yield 71%) existed as a mixture of stereoisomers, and it was determined by coupling constant measurements between H7 and H8 that the major isomer had a *syn* relationship between the two newly-formed stereocenters [6] Since the configuration at the corresponding centers (namely, C7 and C8) in the natural product was *anti*, this served as an excellent test of our methodology Under acidic or basic conditions, we presumed that 5 could be cyclized to form the hemiacetal 6 and that it would be

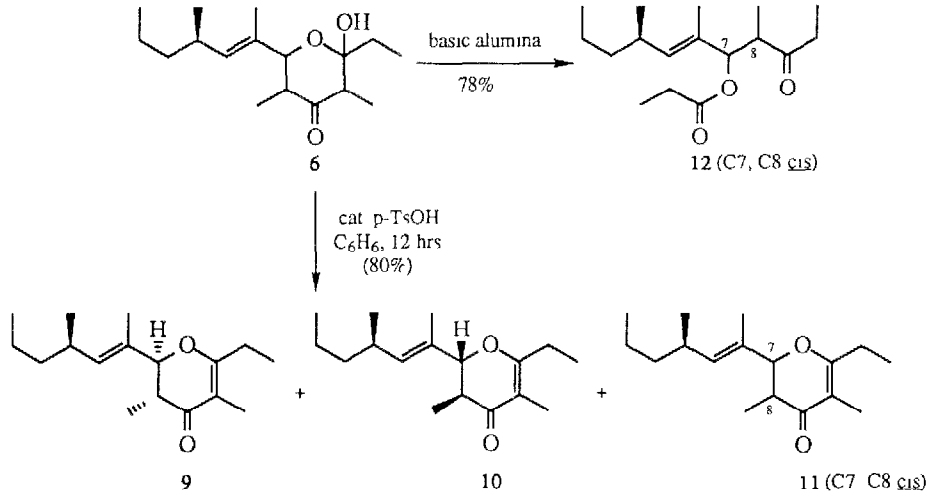
possible to equilibrate 6 to the most thermodynamically favorable hemiacetal isomers 7 and 8, one of which would correspond to the stereochemistry of the natural product or its enantiomer

Scheme I Strategy of Thermodynamic Synthesis of 1



However, attempts to convert 5 to the hemiacetals 7 and 8 under acidic, basic, and buffered conditions resulted in the exclusive formation of dihydropyrones 9-11 (typical results are shown in Scheme II), where dehydration occurred faster than equilibration of the remaining centers When 5 was treated with a catalytic amount

Scheme II Equilibration of 6

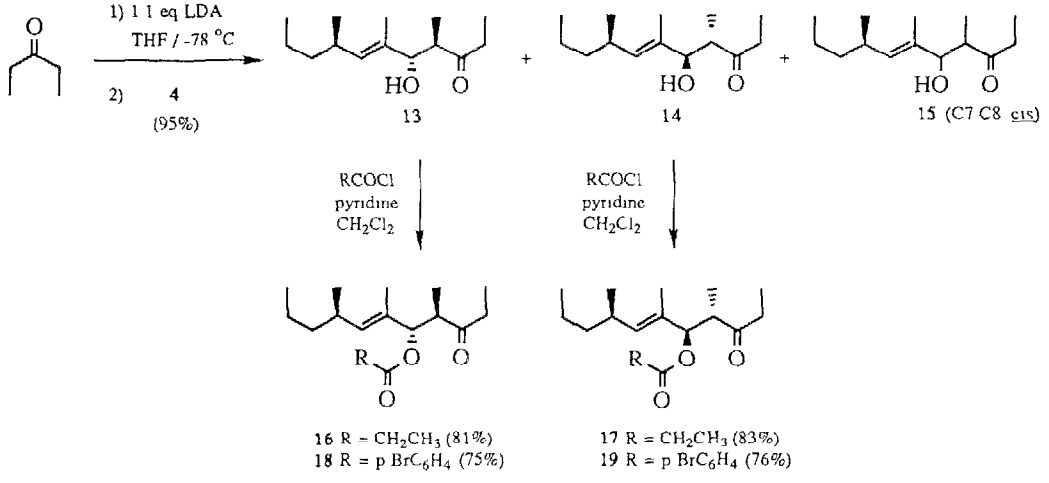


of p-toluenesulfonic acid in benzene for 12 hours, the dihydropyrone isomers were obtained as a 1 1 3 mixture of

9 **10** **11**, where **11** represented an inseparable mixture of the *cis* isomers (overall yield 80%) Flash chromatography of **5** through a column of basic alumina gave **12** in 78% yield, which can be derived from **6** by a retro-Claisen condensation process Comparison of the ^{1}H NMR spectra of **12** and the naturally-occurring **2** clearly showed that they were *not* the same

Subsequently, we began the synthesis of **2** via the pathway shown in Scheme III Aldol condensation of the chiral aldehyde **4** with the lithium enolate of 3-pentanone gave **13**-**15** in 95% yield in the ratio of 3 5 3 5 2 of **13** **14** **15** The aldol adducts **13** and **14** were separated and converted to the propionate esters **16** (81% yield) and **17** (83% yield), respectively, under standard acylating conditions Comparison of ^{1}H and ^{13}C spectra in C_6D_6 of **16** and **17** revealed that the only difference between these diastereomers was the position of two multiplet resonances in the region between δ 1 4 and δ 1 0 in the ^{1}H spectrum In the spectrum of **16**, these resonances appeared as two discrete multiplets of one proton (δ 1 30) and three protons (δ 1 21), but in **17** they were overlapped into one multiplet consisting of four protons (δ 1 12) The ^{1}H spectrum of the natural product **2** was identical to that of **16**

Scheme III Synthesis of Metabolite 2



Optical rotations of **16** ($[\alpha]_D$ = -19 4 °) and **17** ($[\alpha]_D$ = -10 3 °) indicated that these were in the same enantiomeric series as **2** ($[\alpha]_D$ = -7 1 °) The absolute configuration of the natural and synthetic products were assigned by utilizing the exciton chirality method for determination of the absolute configuration of acyclic allylic alcohols [7] The p-bromobenzoate derivatives **18** (75% yield) and **19** (76% yield) were synthesized from the alcohols **13** and **14** under standard acylating conditions Circular dichroism spectra of both esters taken in MeOH disclosed that **18** showed a positive Cotton effect ($\Delta\varepsilon$= +18 9), while **19** exhibited a negative Cotton effect ($\Delta\varepsilon$= -17 7) Therefore, in accordance with non-empirical rules, the configuration of C7 was designated as S in **18** and R in **19** C8 of **2** could now be assigned as R, and so the absolute configurations of the three centers were established as 4(R),7(S),8(R) Since **1** can be converted to **2**, it is reasonable to assign **1** the structure of **7**

In conclusion, attempts to synthesize 1 using a concomitant cyclization-thermodynamic multiple equilibration method resulted in the exclusive formation of dihydropyrones However, we have successfully synthesized 2 in a straightforward fashion and determined the relative stereochemistry of the remote stereocenter as well as the absolute stereochemistry of these metabolites

Acknowledgements. We wish to thank Prof D J Faulkner and Mr Norman Pratt for helpful discussions U N S also wishes to thank the Howard Hughes Foundation for an Undergraduate Summer Research Stipend

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(Received in USA 29 July 1991, accepted 14 November 1991)