Tetrahedron Letters,Vol.26,No.32,pp 3749-3752,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

PREPARATION OF THE CDE-RING SYSTEM OF PLEUROTIN AND GEOGENINE VIA A STEREOSELECTIVE FREE RADICAL CYCLIZATION

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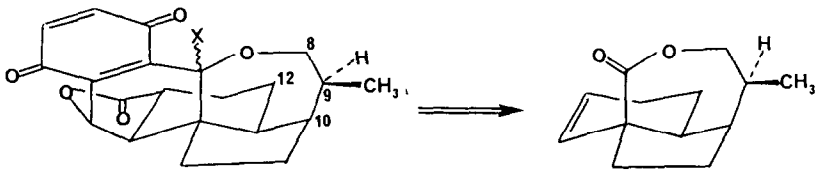
Summary: A synthesis of lactone **3**, a projected intermediate in an approach to pleurotin (**1**)and geogenine (**2**), is described. The trans-perhydroindan nucleus is constructed using a stereoselective free radical cyclization (**5** → **9**).

Pleurotin (**1**)[1] and geogenine (**2**)[2] are structurally related quinoid natural products which exhibit pharmacological properties[3] which may be a result of bioreductive activation.[4] We have undertaken a synthesis of these molecules in which lactone **3** is projected to be a key intermediate. This communication describes a direct synthesis of **3** which features a remarkable stereoselective free radical cyclization.

The synthesis of **3** begins with aldehyde **4**, prepared in four steps (54% overall) from benzoic acid as described previously.[5] Treatment of **4** with 1-(carbethoxy)ethylidene triphenylphosphorane gave ester **5** (mp 74-76°C; 94%) after purification.[6] Free radical cyclization of **5** (nBu$_3$SnH, AIBN, benzene, 60°C) gave perhydroindans **6**(4%), **7**(4%), **8**(4%) and **9**(81%) after separation by silica gel chromatography.[7] The structure of **9** (mp 76-78°C) was established by X-ray crystallography[8] and the relationships between **6** and **7** (**8** and **9**) were established by epimerization experiments (NaOEt, EtOH).

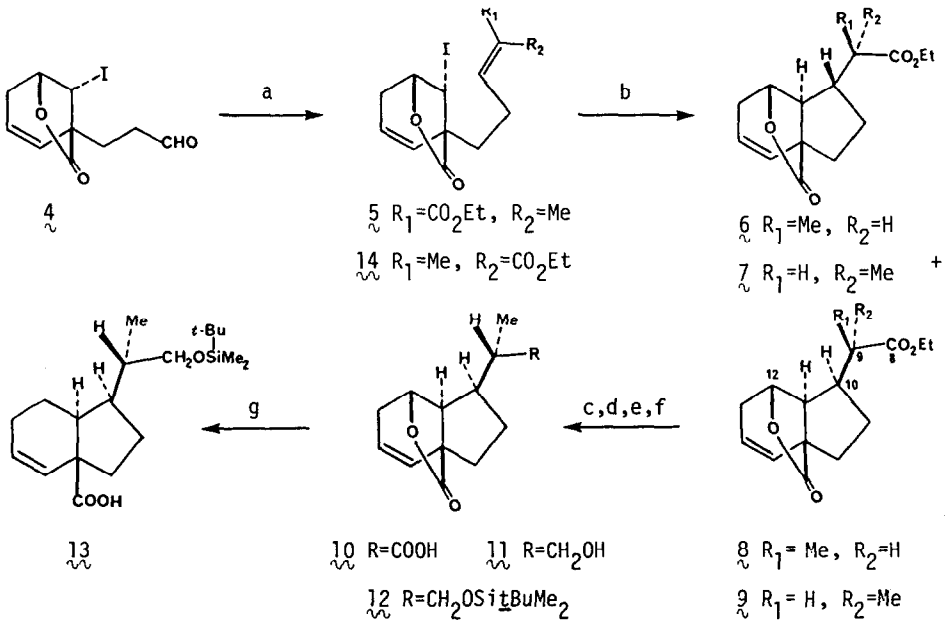
With the perhydroindan nucleus of **3** intact, we turned to adjustment of oxidation state at C(8) and C(12). Treatment of ester **9** with lithium hydroxide in aqueous methanol gave acid **10** (mp 170-171°C; 89%) which was converted to alcohol **11** [(i) $(COCl)_2$, (ii) $NaBH_4$; mp 103-107°C; 91%][9] and subsequently ether **12** [TBDMSCl, Et_3N, DMF; mp 56-58°C; 98%].[10] The C(12)-O bond was



1 X = β-H

2 X = α-H

3



4

5 R_1=CO_2Et, R_2=Me

14 R_1=Me, R_2=CO_2Et

6 R_1=Me, R_2=H

7 R_1=H, R_2=Me +

13

10 R=COOH 11 R=CH_2OH

12 R=$CH_2OSi\underline{t}BuMe_2$

8 R_1= Me, R_2=H

9 R_1= H, R_2=Me

(a) Ph_3P=$C(CH_3)CO_2Et$, CH_2Cl_2 (b) $\underline{n}Bu_3SnH$, AIBN, PhH, 60°C (c) LiOH, H_2O-MeOH (d) $(COCl)_2$ (e) $NaBH_4$ (f) $\underline{t}BuMe_2SiCl$, Et_3N, DMF (g) Li, $EtNH_2$

then reduced using lithium in ethylamine to afford acid **13** (mp 110-112.5°C; 40%).[11,12] Finally, treatment of **13** with oxalyl chloride in benzene at room temperature gave lactone **3** in 70% yield.

From a stereochemical standpoint, we felt that the highly selective conversion of **5** to **9** was interesting and decided to determine whether olefin geometry was a factor in the stereochemical course of this cyclization. Thus, treatment of **4** with the appropriate phosphorane in methanol[13] gave esters **5** (65%) and **14** (15%), which were separated by column chromatography. Treatment of **14** with $\underline{n}Bu_3SnH$ and AIBN under conditions identical to those used with **5** gave **6** (12%), **7** (15%), **8** (1.3%) and **9** (37%) after chromatographic separation.[14] Thus, although olefin geometry does influence the stereochemical outcome at C(10), it does not play a significant role at C(9).[15]

In summary, a direct route to tricyclic lactone **3** has been developed. The synthesis provides an example of the utility of free radical cyclizations in the construction of

trans-perhydroindans.[16] In addition, the stereoselectivity observed in the cyclization of **5** suggests that this approach might find use in the preparation of selected terpenoids which require control of sidechain stereochemistry.[17]

Acknowledgment. We thank the National Science Foundation for their support of this research. We thank Mr. Richard Weisenberger for recording mass spectra at The Ohio State University Chemical Instrument Center.

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[‡]Alfred P. Sloan Foundation Fellow, 1983-1985

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6. All new compounds reported herein gave ^{1}H-NMR, IR, MS, and HRMS or combustion analytical data in accord with the assigned structures.

7. The C(12) protons in **6-9** appeared as broad singlets at δ 4.61, 4.70, 4.58, and 4.88, respectively. A 500 MHz ^{1}H-NMR analysis of a pure mixture of cyclization products, prior to separation, gave 16:1:1 ratio of **9:7:6+8**. The yields quoted in the text are of isolated material. The stereochemical assignments for **6** and **7** may be reversed.

8. We thank Dr. Judith Gallucci for determining this structure at The Ohio State University Chemistry Department X-Ray Crystallography Facility.

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12. In addition to **13**, material in which the carbon-carbon double bond had been reduced was obtained in 8% yield.

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14. A 500 MHz ^{1}H-NMR analysis of a mixture of cyclization products, prior to separation, gave a 3.2:2.2:1 ratio of **9**:**7**:**6**+**8**.

15. For another example where olefin geometry dramatically affects the stereochemical course of an intramolecular free radical conjugate addition see Wilcox, C. S.; Thomasco, L. M. J. Org. Chem. **1985**, 50, 546.

16. For another recent example see Stork, G.; Kahn, M. J. Am. Chem. Soc., **1985**, 107, 500.

17. For example see Nozoe, S.; Morisaki, M. J. Chem. Soc., Chem. Commun. **1969**, 1319. Taber, D. F.; Krewson, K. R.; Raman, K.; Rheingold, A. L. Tetrahedron Lett. **1984**, 5283 and references cited therein.

(Received in USA 2 May 1985)