Tetrahedron Letters Vol. 21, pp 3127 - 3130 ©Pergamon Press Ltd. 1980. Printed in Great Britain

DIRECT STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-SEYCHELLENE

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Abstract: A very short total synthesis of seychellene is described in which the tricyclic ring system is prepared by a cycloaddition-Michael reaction approach.

Due to its interesting tricyclic structure, the plant sesquiterpene, seychellene <u>1</u>,³ has ofte been used as a model compound on which to test new general methods of synthesis. Six syntheses⁴⁻⁹ have been reported since the pioneering work of Piers in 1969.⁴ In addition, several other possib routes to the intriguing tricyclo[5.3.1.0^{3,8}]undecane ring system have been attempted.^{10,11} Recen we reported⁸ a very high yielding (20% overall) synthesis of seychellene, one step of which - the reduction of a double-bond on an acyclic side-chain - was completely nonspecific in its stereochemical course, yielding an equimolar mixture of the two possible stereoisomeric products. We no wish to describe a very direct, stereoselective total synthesis of seychellene (Scheme I), in whic the nonselective reduction has been essentially eliminated but at the expense of the overall yield

From the outset of this project, it was envisioned that the tricyclic dione <u>B</u> would be an extremely useful intermediate for the synthesis of seychellene. It was assumed that the two carbony groups could be readily differentiated by virtue of their dissimilar steric environments, for example, by their reactivity toward nucleophiles. Since it seemed reasonably certain that seychelle could be easily produced from <u>B</u>, this dione then became the immediate synthetic target.

As an immediate precursor of the dione $\underline{8}$, the enol ether $\underline{6}$ was chosen. An internal Lewis acidcatalyzed cyclization by the method of Mukaiyama,¹² corresponding to an endo-6-trig cyclization in



Baldwin's terms, ¹³ should produce the desired dione <u>8</u>. In addition, compound <u>6</u> was potentially available in one step by the cycloaddition of the readily available components 3 and 5, thus m_i this synthetic route particularly attractive. In the event, the diene $\underline{3}$, prepared as described previously 8 from the enone 2, was allowed to react at room temperature for 4 h with divinyl ket 5, prepared by the double dehydrohalogenation of the ketone 4, 14 to afford a 94% isolated yield the desired enone enol ether 6. Treatment of this compound with TiCl₄ in CH_2Cl_2 at -78°C for 10 afforded, after preparative layer chromatography on silica gel (ether:hexane, 1:2) or preparat HPLC, a 5% yield of the crystalline dione 8. 15 The major products of this reaction were those formed by retro-Michael reaction, i.e., path b in the intermediate A, namely the 6-substituted cyclohexenone 7, 2,3-dimethylcyclohexenone 2, and polymeric material. It is clear from this e: ment that in contrast to acyclic cases, the desired endo-6-trig cyclization 13 is not very favor probably due to the additional constraints of the bicyclic structural framework. In only one (formation is the vinyl group of the enone properly oriented for cyclization to occur (path a), while in many conformations the carbonyl group is aligned so that retro-Michael reaction can ∞ (path b). A great many attempts were made to increase the yield of this key cyclization step, namely using other acids (SnCl₄, AlCl₃, BF₃, HF, TFA), different temperatures (-100°C to 25°C) various solvent combinations. However, it has not yet been possible to obtain consistently mon than 5% of the purified dione 8 in this reaction.

The synthesis was completed as originally planned as follows. Reaction of the dione with meilithium at -78°C for 8 h then 0°C for 2 h gave the keto alcohols $\underline{9}^{16}$ in good yield (75-80% iso'ed). This mixture was dehydrated with POCl₃/pyridine to afford a mixture of the endo- and exocyclic olefins, <u>10</u> and <u>11</u>, respectively. in an overall yield of 46% based on dione <u>8</u>. The endocyclic olefin <u>10</u> greatly predominated, constituting about 85% of the mixture.¹⁷ Direct hydrogetion of the olefin mixture furnished an 83% yield of an 80:20 mixture of norseychellanone $\underline{12}^{18}$ epinorseychellanone <u>13</u>. Thus, as expected, postponement of the olefin reduction step until after cyclization greatly improved the stereoselectivity of this hydrogenation in favor of the desire isomer <u>12</u>. The final conversion of norseychellanone <u>12</u> to seychellene <u>1</u> was accomplished by the method of Piers, thus completing a very short, seven-step synthesis of seychellene <u>1</u> from the diene <u>3</u> and the dienone <u>5</u> in an overall yield of 1.4%.

Acknowledgment: We thank the UCLA Committee on Research for partial support of this research. Bruker 200-MHz NMR spectrometer was purchased with funds provided by a major instrument grant from the National Science Foundation.



80:20

Scheme I

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- 15. Spectral and analytical data: mp 120°C; Calcd: C, 75.69; H, 8.80; Found: C 75.55; H, 8.84; ¹H NMR (CDCl₃ 200 MHz); δ 0.87 (3H, s), δ 1.10 (3H, s), δ 1.6-2.5 (12H, m); IR (CDCl₃): 2970 cm⁻¹, 1720 cm⁻¹; MS (16ev): 206 (M+), 124, 96. Also the ¹³C NMR was fully consistent with the proposed structure.
- 16. One stereoisomer of <u>9</u> greatly predominates (about 90%) over the other, but we do not have enough data to assign its stereochemistry.
- 17. The two isomers could be easily distinguished in the crude reaction mixture by the chemica shift of their olefinic protons (10: δ 5.02; 11: δ 4.52).
- 18. Our synthetic norseychellanone <u>12</u> was identical (200 MHz ¹H NMR) to an authentic sample kindly provided by Professor E. Piers.

(Received in USA 11 March 1980)