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DIRECT STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-SEYCHELLENE[1]

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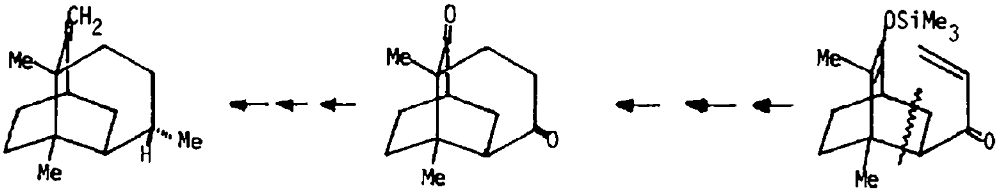
Abstract: A very short total synthesis of seychellene is described in which the tricyclic ring system is prepared by a cycloaddition-Michael reaction approach.

Due to its interesting tricyclic structure, the plant sesquiterpene, seychellene 1,[3] has ofte been used as a model compound on which to test new general methods of synthesis. Six syntheses[4-9] 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 reported[8] 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 8 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 8, this dione then became the immediate synthetic target.

As an immediate precursor of the dione 8, the enol ether 6 was chosen. An internal Lewis acid-catalyzed cyclization by the method of Mukaiyama,[12] corresponding to an endo-6-trig cyclization in



1 8 6

Baldwin's terms,[13] should produce the desired dione 8. In addition, compound 6 was potentially available in one step by the cycloaddition of the readily available components 3 and 5, thus m this synthetic route particularly attractive. In the event, the diene 3, prepared as describe previously[8] from the enone 2, was allowed to react at room temperature for 4 h with divinyl ke 5, prepared by the double dehydrohalogenation of the ketone 4,[14] to afford a 94% isolated yiel the desired enone enol ether 6. Treatment of this compound with $TiCl_4$ in CH_2Cl_2 at -78°C for 1 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 favo 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 o (path b). A great many attempts were made to increase the yield of this key cyclization step, namely using other acids ($SnCl_4$, $AlCl_3$, BF_3, HF, TFA), different temperatures (-100°C to 25°C) various solvent combinations. However, it has not yet been possible to obtain consistently mo than 5% of the purified dione 8 in this reaction.

The synthesis was completed as originally planned as follows. Reaction of the dione with me lithium at -78°C for 8 h then 0°C for 2 h gave the keto alcohols 9[16] in good yield (75-80% iso ed). This mixture was dehydrated with $POCl_3$/pyridine to afford a mixture of the endo- and exo cyclic olefins, 10 and 11, respectively, in an overall yield of 46% based on dione 8. The end cyclic olefin 10 greatly predominated, constituting about 85% of the mixture.[17] Direct hydrog tion of the olefin mixture furnished an 83% yield of an 80:20 mixture of norseychellanone 12[18] epinorseychellanone 13. Thus, as expected, postponement of the olefin reduction step until aft cyclization greatly improved the stereoselectivity of this hydrogenation in favor of the desir isomer 12. The final conversion of norseychellanone 12 to seychellene 1 was accomplished by th method of Piers,[4] thus completing a very short, seven-step synthesis of seychellene 1 from the diene 3 and the dienone 5 in an overall yield of 1.4%.

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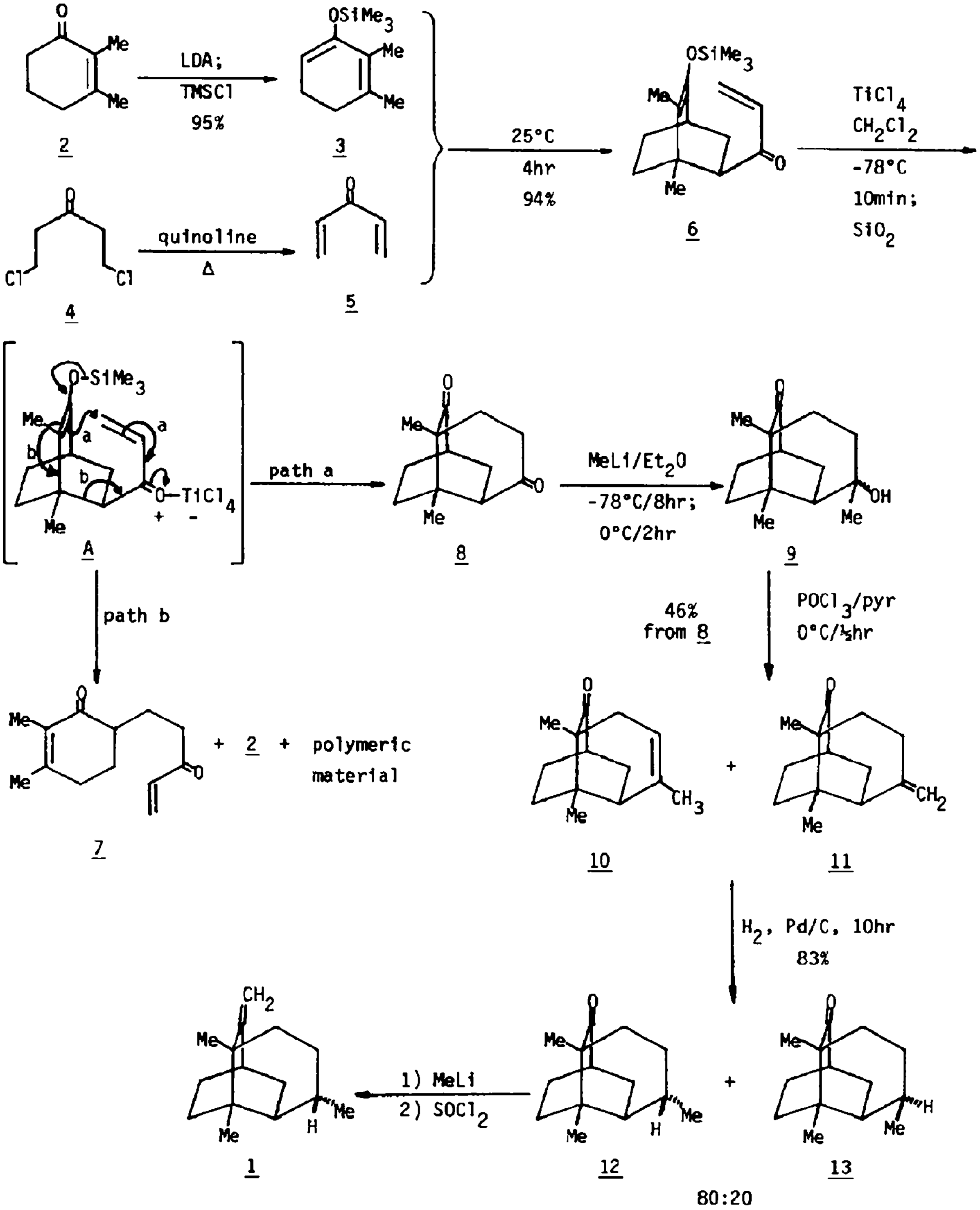
2
LDA; TMSCl 95%
3
4
quinoline Δ
5
25°C 4hr 94%
6
TiCl$_4$ CH$_2$Cl$_2$ -78°C 10min; SiO$_2$
A
path a
8
MeLi/Et$_2$O -78°C/8hr; 0°C/2hr
9
path b
7
+ 2 + polymeric material
46% from 8
POCl$_3$/pyr 0°C/½hr
10
11
H$_2$, Pd/C, 10hr 83%
1
1) MeLi 2) SOCl$_2$
12
13
80:20

Scheme I

REFERENCES AND NOTES

1. This work was presented in part at the 1979 Pacific Conference on Chemistry and Spectroscopy (15th Western ACS Regional Meeting), Pasadena, CA, October 1979, Abstract 71.
2. Camille and Henry Dreyfus Teacher-Scholar 1978-83; Fellow of the Alfred P. Sloan Foundation, 1979-1981.
3. G. Wolff and G. Ourisson, *Tetrahedron*, **25**, 4903 (1969) and references therein.
4. E. Piers, R. W. Britton, and W. de Waal, *J. Am. Chem. Soc.*, **93**, 5113 (1971); *J.C.S. Chem. Comm.*, 1069 (1969).
5. K. J. Schmalzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970); R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **34**, 2358 (1969).
6. N. Fukamiya, M. Kato, and A. Yoshikoshi, *J.C.S. Chem. Comm.*, 1120 (1971).
7. G. Frater, *Helv. Chim. Acta*, **57**, 172 (1974).
8. M. E. Jung and C. A. McCombs, *J. Am. Chem. Soc.*, **100**, 5207 (1978).
9. K. Yamada, Y. Kyotani, S. Manabe, and M. Suzuki, *Tetrahedron*, **35**, 293 (1979); *Bull. Chem. Soc. Japan*, **51**, 3405 (1978).
10. K. D. White and W. Reusch, *Tetrahedron*, **34**, 2439 (1978).
11. D. Spitzner, *Tetrahedron Lett.*, 3349 (1978); *Angew. Chem.*, **90**, 213 (1978).
12. K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, 1223 (1974); T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
13. J. E. Baldwin, *et al.*, *J.C.S. Chem. Comm.* 734, 736 (1976); 77, 233 (1977).
14. G. Baddeley, H. T. Taylor, and W. Pickels, *J. Chem. Soc.*, 124 (1953); N. Jones and H. T. Taylor, *ibid.*, 1345 (1961).
15. Spectral and analytical data: mp 120°C; Calcd: C, 75.69; H, 8.80; Found: C 75.55; H, 8.84; ^{1}H NMR ($CDCl_3$ 200 MHz); δ 0.87 (3H, s), δ 1.10 (3H, s), δ 1.6-2.5 (12H, m); IR ($CDCl_3$): 2970 cm^{-1}, 1720 cm^{-1}; MS (16ev): 206 (M+), 124, 96. Also the ^{13}C NMR was fully consistent with the proposed structure.
16. One stereoisomer of 9 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 12 was identical (200 MHz ^{1}H NMR) to an authentic sample kindly provided by Professor E. Piers.

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