Tetrahedron Letters,Vol.28,No.3,pp 303-306,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

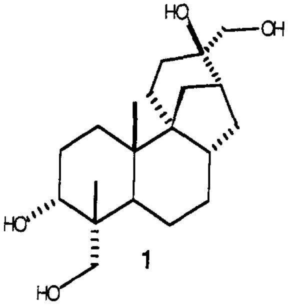
STEREOCONTROL OF THE METAL-AMMONIA REDUCTION: FORMATION OF EITHER CIS- OR TRANS-FUSED DECALONES FROM A COMMON INTERMEDIATE.

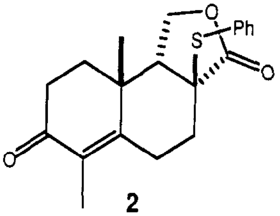
Robert A. Holton* and Robert M. Kennedy

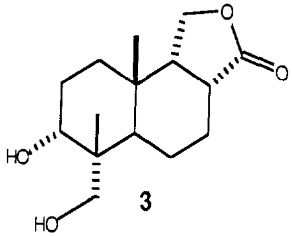
Dittmer Laboratory of Chemistry[1]
The Florida State University
Tallahassee, Florida 32306
USA

Summary: Octalone 2 is reduced by lithium-ammonia to the cis-fused decalone, whereas octalone 7 undergoes lithium-ammonia reduction to provide exclusively the trans-fused isomer.

We have recently described a new stereospecific annulation,[2] developed during the course of our studies directed toward aphidicolin (1)[3] total synthesis.[4] This methodology has enabled us to prepare, in two synthetic operations and 67% overall yield, the octalone 2[2] as a model for the aphidicolin AB ring system.

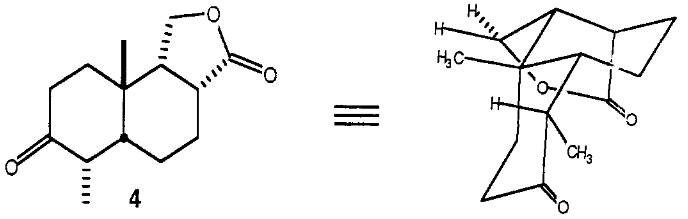

1


2


3

In an extension of this model study, we set out to explore the conversion of 2 into the diol 3, having A ring functionality identical to that present in 1. We envisioned that the 2 → 3 conversion could be accomplished through lithium-ammonia reduction followed by enolate trapping similar to the sequence which has previously been employed in several aphidicolin syntheses.[4a,b,d] Furthermore, we anticipated that lithium-ammonia reduction of 2 would also desulfurize C-8 to form the lactone enolate which would serve to protect the lactone from overreduction.

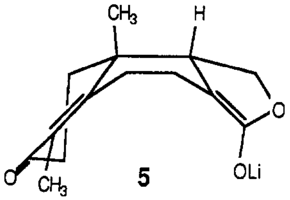
In the event, enone 2 was treated with 4 mol equiv of lithium in 5:1 ammonia:THF solution containing 0.85 equiv of t-butanol, first at -78°C for 15 min, then at -33°C for 15 min. Excess lithium was quenched with isoprene and the mixture was subsequently treated with aqueous sodium bicarbonate to provide keto ester 4,[5] mp 200-202°C, in 95% yield.[6] The ^{1}H NMR spectrum of 4 showed H4, upon irradiation of the C-4 methyl protons, as a doublet at δ2.92 with a 4Hz coupling constant. Upon irradiation of the angular (C-10) methyl protons, an NOE enhancement of the C-12α proton was observed. This latter observation is possible only if the C-10 methyl group is equatorial to ring B. Taken together, these results clearly demonstrate that ketone 4, to our surprise, has the cis AB ring fusion as shown below.



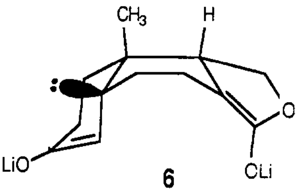
4

Although unusual, several examples of the formation of cis-fused decalones from lithium-ammonia reductions of octalones have been observed.[7] In some of these cases, the B ring is constrained to adopt a boat conformation by the presence of a bulky β substituent at C8.[7a] We rationalize that, in the reduction of 3, the enolate 5 may be initially produced from a rapid reductive desulfurization. Examination of molecular models indicates that the B ring of 5 must adopt a boat conformation. In this case, further reduction would give trianion 6 which would be expected to undergo protonation at C5 from the convex β face to give 4.

According to this rationale, formation of the lactone enolate prior to reduction of the enone is solely responsible for the ultimate protonation at C5 from the β face to give cis ring fusion. Therefore, reduction of lactone 7 would be predicted to follow the more conventional course leading to the trans AB ring fusion.

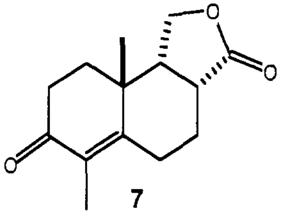


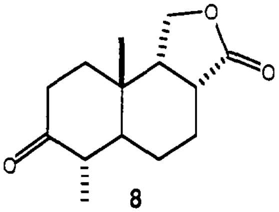
5

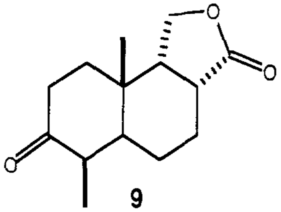


6

Desulfurization of 2 with Raney nickel gave 7[5] in 88% yield.[6] Lithium-ammonia reduction of 7 under the conditions described above gave a single lactol isomer which was oxidized directly (JONES) to provide lactone 8[5] in 72% overall yield.[6] The ^{1}H NMR spectrum of 8 showed H4, upon irradiation of the C4 methyl protons, as a doublet at δ2.33 with an 11Hz coupling constant, consistent with a trans diaxial relationship of H4 and H5. Further support for this structural assignment was provided by catalytic hydrogenation (5% Pd/C; EtOH) of 7 to give keto lactone 9,[5] the C4 epimer of 8. In the presence of potassium *t*-butoxide, 9 isomerized to provide 8 quantitatively. Apparently, hydrogenation of 7 occurred from the α face to give the trans-fused decalone derivative having an axial (β) C4 methyl group.

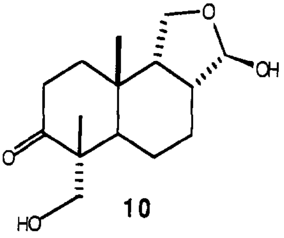

7

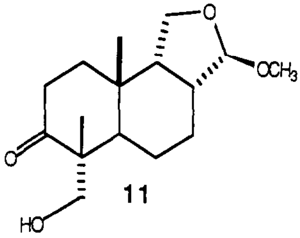

8

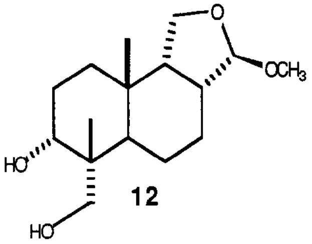

9

These observations provide a unique demonstration of the influence of substrate conformation on the stereochemical outcome of lithium-ammonia reduction of octalone derivatives. To our knowledge, this is the first example in which a common intermediate can serve as precursor for the exclusive formation of either cis- or trans-fused decalone via a lithium-ammonia reduction.

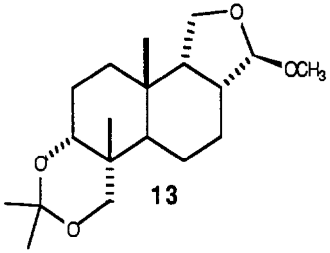
Completion of the aphidicolin model study was carried out in the following way. Lithium-ammonia reduction of 7 followed by *in situ* trapping of the enolate with formaldehyde provided ketol 10[5] in 60% yield.[6] The lactol was converted quantitatively to acetal 11[5] through the action of a methanolic solution of pyridinium *p*-toluenesulfonate. Reduction of 11 with L-selectride gave only diol 12.[5] The stereochemistry at C3 and C4 in 12 was confirmed by ^{1}H NMR analysis of the bis acetate. Furthermore, 12 could readily be converted to aceton-


10


11



12



13

ide 13,[5] whose ^{1}H NMR spectrum was characteristically similar to the acetonide derived from aphidicolinone.

The application of these findings to aphidicolin total synthesis will be reported in due course.

Acknowledgment. We thank the Public Health Service for their generous financial support of our programs.

References and Notes

(1) A portion of this work was carried out at Virginia Polytechnic Institute and State University.

(2) Krafft, M.E.; Kennedy, R.M.; Holton, R.A. Tetrahedron Lett. 1986, 27, 2087.

(3) (a) Jarvis, J.A.J.; Neidle, S.; Brundet, K.M.; Dalziel, W.; Hesp, B. Chem. Commun. 1972, 1027; (b) Dalziel, W.; Hesp, B.; Stevenson, K.M.; Jarvis, J.A.J. J. Chem. Soc. Perkin I 1973, 2841.

(4) Total syntheses: (a) McMurry, J.E.; Andrus, A.; Musser, J.H.; Johnson, M.A. Tetrahedron 1981, 37, 319; (b) Trost, B.M.; Nishimura, Y.; Yamamoto, K. J. Am. Chem. Soc. 1979, 101, 1328; (c) Corey, E.J.; Tius, M.A.; Das, J. Ibid. 1980, 102, 1742; (d) Ireland, R.E.; Godfrey, J.D.; Thaisrivongs, S. Ibid. 1981, 103, 2446; (e) Van Tamelen, E.E.; Zawacky, S.R.; Russel, R.K.; Carlson, J.G. Ibid. 1983, 105, 142; (f) Bettollo, R.M.; Tagliatesta, P.; Lupi, A.; Bravetti, D. Helv. Chem. Acta. 1983, 66, 1922; other approaches to the total synthesis: (g) Kametani, T.; Honda, T.; Shiratori, Y.; Fukumoto, K. Tetrahedron Lett. 1980, 1665; (h) Cargill, R.L.; Bushey, D.F.; Dalton, J.R.; Prasad, R.S.; Dyer, R.D.; Bonder, J. J. Org. Chem. 1981, 46, 3389.

(5) Characterized by IR, NMR, and combustion or high resolution mass spectral analysis.

(6) Yields refer to isolated, spectrally and chromatographically homogeneous material.

(7) (a) For a review, see Caine, D. Org. Reactions 1976, 23, 1; (b) Sasaki, S.; Grieco, P.A.; Huffman, J.C.; Callant, P., Imamura, P.M. J. Org. Chem.; 1985, 50, 4880; (c) Fringuelli, F,; Taticchi, A.; Fernandez, F.; Kirk, D.N.; Scopes, M. J. Chem. Soc. Perkin I 1974, 1103; (d) House, H.O. "Modern Synthetic Reactions"; W.A. Benjamin: Menlo Park, CA, 1970; p. 179.

(Received in USA 25 July 1986)