Tetrahedron Letters, Vol.30, No.4, pp 433-436, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

FURTHER INVESTIGATIONS OF THE TYPE II DIELS-ALDER ROUTE TO THE BICYCLIC CORE OF ESPERAMICIN/CALICHEMICIN REVEAL A REGIOCHEMICAL MISASSIGNMENT: META VS. PARA SELECTIVITY

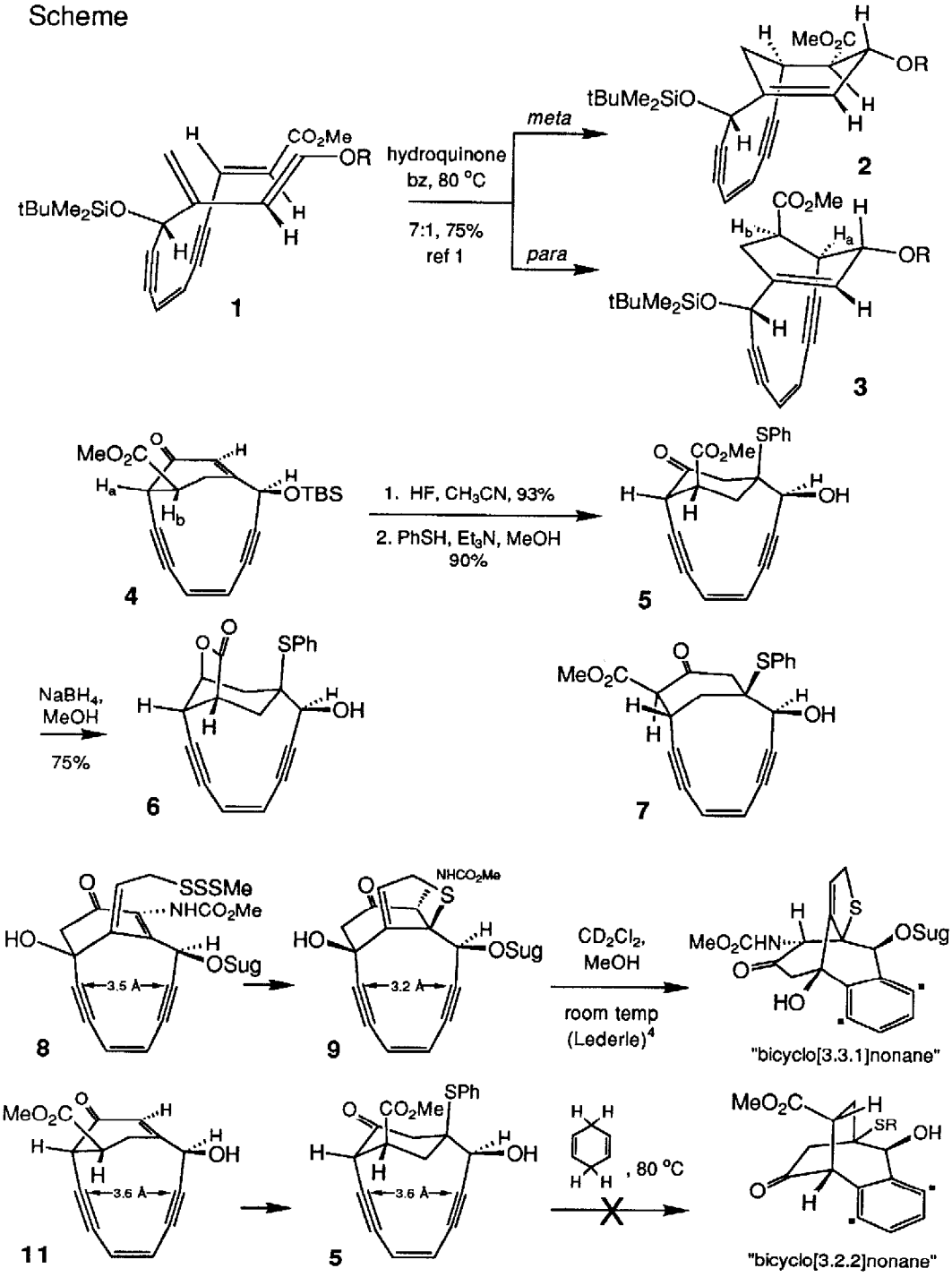
Stuart L. Schreiber and Laura L. Kiessling*
Sterling Chemistry Laboratory
Yale University, New Haven, Connecticut 06511

Abstract The chemistry of an IMDA reaction product has been investigated and reveals that the regiochemical outcome of the cycloaddition was incorrectly assigned in the original report. The product of this reaction is a skeletal isomer of the esperamicin/calichemicin bicyclic core structure.

A communication from this laboratory described the synthesis of the bicyclic core of the esperamicin/calichemicin class of antibiotics.[1] A key feature of this route was the type II intramolecular Diels-Alder reaction of **1** that was reported to proceed in a regiospecific fashion to provide **2**. The reported regiochemistry was in accord with the outcome of other type II Diels-Alder cycloadditions and the directing properties of the diene and dienophile substituents.[2] Subsequent transformations included the deprotection of the phenolic ether and oxidation of the resultant allylic alcohol to the corresponding enone. Recent investigations of more highly substituted analogues of **1** and products resulting from subsequent transformations of the putative structure **2** have revealed that the original regiochemical assignment of the Diels-Alder reaction of **1** was incorrect. In this Letter, evidence in support of the regioisomeric product **3** is presented. A study of products derived from **3** that contain sp^3-hybridized bridgehead atoms illustrate the reticence of the isomeric ring system to undergo the Bergman cyclization chemistry that is characteristic of the natural products[3,4] and related models.[5,6]

Deprotection of Diels-Alder adducts **3** (R = p-methoxyphenyl, p-methoxybenzyl) with CAN or DDQ and oxidation of the resultant alcohol (tetrapropylammonium perruthenate (cat), NMO)[7] provided the enone **4**. After deprotection of the silyl ether, treatment of this compound with thiophenol in the presence of triethylamine resulted in the formation of a Michael addition product. The original regiochemical assignment of the Diels-Alder reaction led to the belief that the bicyclo[7.3.1]tridecadiynene **7** was in hand. The stability of this compound, particularly with regard to its lack of reactivity in the "Bergman" sense, cast doubt on this assignment.[3-6] Compelling evidence for the alternative structure **5** was obtained when the reduction of the Michael adduct was investigated. Treatment of **5** with sodium borohydride provided a lactone with a carbonyl stretching frequency at 1789 cm^{-1}. Together with additional supportive spectroscopic data,[8] the structure of the lactone can be assigned as **6** in the Scheme.

Scheme


tBuMe2SiO
CO2Me
OR
hydroquinone
bz, 80 °C
7:1, 75%
ref 1
meta
para
MeO2C
OTBS
1. HF, CH3CN, 93%
2. PhSH, Et3N, MeOH
90%
SPh
NaBH4,
MeOH
75%
SSSMe
NHCO2Me
OSug
3.5 Å
3.2 Å
3.6 Å
CD2Cl2,
MeOH
room temp
(Lederle)4
"bicyclo[3.3.1]nonane"
"bicyclo[3.2.2]nonane"
80 °C

In the course of their discovery of the calichemicins, Lederle scientists explored the reactivity of calichemicin γ_1.[4] An important conclusion that was deduced from these studies is that the conversion of the bridgehead trigonal carbon to a tetrahedral carbon in the bicyclic core serves as the priming mechanism for the coupling of the enediyne to a benzene diyl. It was suggested that the Michael adduct **9** (from **8**) undergoes facile (rt) coupling to the diradical **10** as evidenced by the incorporation of two deuterium atoms from the CD_2Cl_2 solvent. In contrast to the natural system and related model compounds, the skeletal isomer **5** (from **11**) was found to be stable to conditions of refluxing 1,4-cyclohexadiene (solvent, 80 °C). Inspection of computer generated models of **9** and **5** indicates a dramatic difference in the geometry of the enediyne moieties of these compounds (Scheme) that is fully consistent with their contrasting reactivities. We have found, however, that the introduction of certain substituents about the cyclohexyl ring of **5** result in analogues that are capable of undergoing the Bergman cyclization, affording products with the benzannulated bicyclo[3.2.2]nonane skeleton of **12**. An analysis of structure-reactivity relationships within this series is underway. Details of theses investigations will be reported later.

Can the Diels-Alder reaction be coaxed into following the regiochemical path that leads to the esperamicin/calichemicin bicyclic core? Our current studies seek to address this question and related issues.

Acknowledgements: Financial support of this project was provided by the NIH and NSF. We thank Dr. Frank J. Schoenen and John A. Porco, Jr. for important contributions.

References and Footnotes

1. Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.
2. Shea, K. J.; Fruscella, W.M.; Carr, R. C.; Burke, L. D.; Cooper, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 447.
3. esperamicins A_1, A_2, and A_{1b}: Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saito, K.; Doyle, T.W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.
4. calichemicin γ_1: Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.
5. (a) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921.
   (b) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626.
6. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.
7. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. C. S. Chem Commun.* **1987**, 1625.

8. **3** (R = paramethoxybenzyl): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (d, J =8.6 Hz, 2H, aromatic), 6.85 (d, J = 8.6 Hz, 2H, aromatic), 5.85 (dd, J = 9.7, 2.4 Hz, 1H, -CH=CH-C≡C-CHRR'), 5.74 (dd, J = 9.7, 0.8 Hz, 1H, -CH=CH-C≡C-CH(OTBS)-), 5.54 (br s, -CH=CRR'), 5.20 (br s, 1H, -CHR(OTBS)), 4.59 (d, J = 11.9 Hz, 1H, ArCHHO-), 4.51 (d, J = 11.9 Hz, 1H, ArCHHO-), 3.93 (br s, 1H, -CH(OCH$_2$Ar)-), 3.78 (s, 3H, -CO$_2$CH$_3$), 3.60 (s, 3H, CH$_3$OAr-), 3.60 (m, 1H, -C≡C-CHRR'-H$_a$ in **3**), 2.96 (m, 2H, -CHHCH(CO$_2$CH$_3$)- overlapping with -CH(CO$_2$CH$_3$)-H$_b$ in **3**), 2.65 (m, 1H, -CHHCH(CO$_2$Me)-), 0.89 (s, 9H, -C(CH$_3$)$_3$), 0.12 (s, 3H, -SiCH$_3$), 0.10 (s, 3H, -SiCH$_3$) The assignments (concerning **2** and the (meta)-isomer of **4**) for H$_a$ and H$_b$ were interchanged in the original report.[1]
^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.8 (-CO$_2$Me), 159.3 (aromatic), 142.1 (RR'C=CH-), 129.9 (aromatic), 129.4 (aromatic), 124.3 (RR'C=CH-), 122.5 (-CH=CH-), 121.3 (-CH=CH-), 113.7 (aromatic), 102.3 (-CH=CH-C≡C-), 96.5 ((-CH=CH-C≡C-), 85.7 (-CH=CH-C≡C-), 82.4 (-CH=CH-C≡C-), 71.1 (-C≡C-CH(OTBS)-), 70.2 (-OCH$_2$-), 69.0 (-C=CH-RCHO-), 55.2 (ArOCH$_3$), 51.9 (-CO$_2$CH$_3$), 40.0 (-CH(CO$_2$CH$_3$)-), 33.9 (-C≡C-RCHR'), 25.7 (-CH$_2$CH(CO$_2$CH$_3$)-), 22.7((CH$_3$)$_3$C-), 18.1((CH$_3$)$_3$C-),-5.1(SiCH$_3$).
IR (film) 2201 (w), 1738 (s). MS (EI, 20eV) 492.3 (M$^+$, 2%), 435.2 (20%), 121.1 (100%).
4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (br s, 1H, -RC=CH-CO-), 5.81 (dd, J = 10.0, 2.7 Hz, 1H, -CH=CH-C≡C-CHRR'), 5.74 (dd, J = 10.0, 1.0 Hz, 1H, -CH=CH-C≡C-CH(OTBS)-), 5.28 (d, J = 1.0 Hz, 1H, -CH(OTBS)-), 3.68 (s, 3H, -CO$_2$CH$_3$), 3.62 (m, 1H, -CHH-), 3.58 (m, 1H, -C≡C-CHRR'), 3.25 (dd, J = 6.9, 2.7 Hz, 1H, -CH(CO$_2$Me)-), 3.06 (d, J = 20.5 Hz, 1H, -CHH-), 0.91 (s, 9H, -C(CH$_3$)), 0.15 (s, 3H, -SiCH$_3$), 0.12 (s, 3H, -SiCH$_3$). Irr. of H at δ 5.81 simplifies H at δ 3.58: no change in the signal at δ 3.25.
^{13}C NMR (62.9 MHz, $CDCl_3$) δ 193.3 (-RC=O), 172.1 (-CO$_2$CH$_3$), 160.7 (-RC=CH-C=O), 124.0 (-C=CH-), 121.6 (-C=CH-), 118.7 (-C=CH-), 99.4 (-C≡C-CH(OTBS)-), 93.5 (-C≡C-CH(COR)-), 88.4(-C≡C-CH(OTBS)-), 84.5 (-C≡C-CH(COR)-), 69.1 (-CH(OTBS)-), 52.4 (-OCH$_3$), 42.3 (-CH(COR)-), 39.3 (-CH(CO$_2$CH$_3$)-), 25.6 (-C(CH$_3$)$_3$),18.1 (-C(CH$_3$)$_3$), -4.9 (-SiCH$_3$), -5.1 (-SiCH$_3$).
IR (film) 1738(s), 1731(m), 1694(s). MS (EI, 20eV) 370.2 (M$^+$, 100%).
HRMS calc. 370.1601, found 370.1582.
6: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (m, 2H, aromatic), 7.41 (m, 3H, aromatic), 5.98 (dd, J = 9.8, 0.9 Hz, 1H, -CH=CH-C≡C-CH(OH)-), 5.93 (dd, J = 9.8, 2.4 Hz, 1H, -CH=CH-C≡C-CH(OH)-), 4.72 (m, 1H, -CH(O(CO)R)-), 3.73 (d, J = 0.9 Hz, 1H, -OH), 3.51 (m, 1H, -C≡C-CHR-), 3.08 (dd, J = 15.6, 3.0 Hz, 1H, -CH$_{ax}$H$_{eq}$-CH(CO$_2$R)-), 2.73 (m, 1H, -CH(CO$_2$R)-), 2.36 (dd, J = 16.1, 1.2Hz, 1H, -CH$_{ax}$H$_{eq}$-CH(O(CO)R)-),1.88 (dd, J =15.6, 3.8 Hz, 1H, -CH$_{ax}$H$_{eq}$-CH(CO$_2$R)-), 1.81 (dd, J =16.1, 3.9 Hz, 1H, -CH$_{ax}$H$_{eq}$-CH(O(CO)R)-).
^{13}C NMR (62.9, $CDCl_3$) (partial) δ 138.2 (aromatic), 130.3 (-CH=CH-), 129.4 (-CH=CH-), 128.6 (aromatic), 123.6 (aromatic), 123.2 (aromatic), 96.7 (-CH =CH-C≡C -), 95.1 (-CH=CH-C≡C-), 85.0 (-CH=CH-C≡C-), 83.7 (-CH=CH-C≡C-), 76.3 (-CH(O(CO)R)-), 68.0 (-CH(OH)-), 56.0 (-CH(CO$_2$R)-), 39.1 (-C≡C-CHRR'), 37.1 (-C(SPh)R-), 27.5 (-CH$_2$-), 27.0 (-CH$_2$-).
IR (film) 3604-3249 (br s), 2207 (w) 1789 (s). MS (EI, 20eV) 336.1 (M$^+$, 8%).

(Received in USA 7 November 1988)