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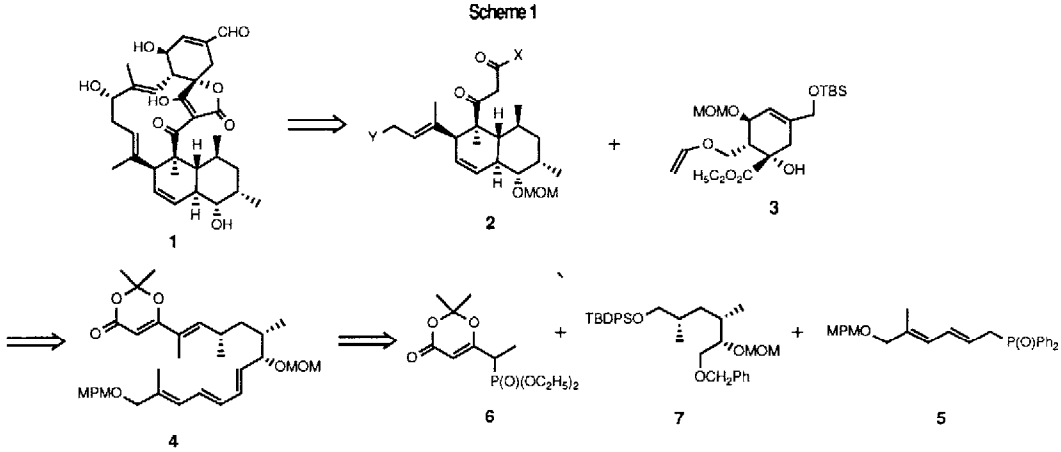
STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF TETRONOLIDE 1. AN ENANTIOSELECTIVE SYNTHESIS OF THE OCTAHYDRONAPHTHALENE UNIT

Robert K Boeckman Jr ,* Thomas E Barta, and Scott G Nelson
Department of Chemistry
University of Rochester
Rochester, New York 14627

Summary *An efficient enantioselective route to the octahydronaphthalene unit present in tetronolide (1), the stereochemically complex aglycone common to the tetrocarcins, a novel group of antitumor substances, is described The sequence employs the intramolecular Diels-Alder reaction to control the relative stereochemistry present on the trans decalin ring system, and incorporates a masked acylating agent which should permit coupling of the two key fragments 2 and 3 as demonstrated by reaction of pentaene 4 with methanol and a model α-hydroxy ester*

The tetrocarcins comprise a group of antitumor antibiotic agents which share a common aglycone, tetronolide **1**.[1] Structurally, tetronolide is related to kijanolide and chlorothricolide, the aglycone units of kijanomycin and chlorothricin, the only other known members of this natural product family.[2,3] These structurally complex aglycones have been the subject of considerable effort directed toward their preparation, although no total synthesis of a naturally-occurring member of this class has yet been completed.[4] In accord with our interest in developing stereoselective variants of the intramolecular Diels-Alder cycloaddition, we chose tetronolide to test the scope of this methodology We conceived a convergent synthetic

Scheme 1

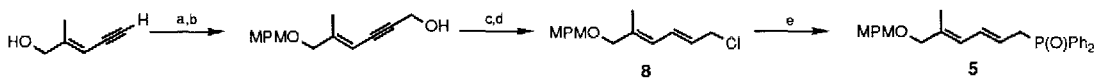


strategy (Scheme 1), whose implementation required the preparation, in enantiomerically pure form, and union of two key synthons comprising the octahydronapthalene **2** and cyclohexene **3** subunits of **1** or precursors thereof Herein, we describe the development of a suitable route to pentaene **4**, an enantiomerically pure precursor of **2**.[5,6]

The advantages of employing a [4+2] cycloaddition to control the relative stereochemistry of centers present on the decalin framework of **2** was recognized early on, and this strategy has been employed by several groups.[7,8] However, our approach differs significantly in the manner

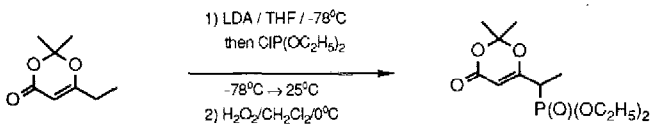
by which the major fragments will be joined, since in all other studies to date the major subunits are to be joined in a separate step, whereas we envisioned the coupling process in tandem with the intramolecular [4+2] cycloaddition. Thus, the required substrate for construction of **2** becomes pentaene **4**, whose synthesis is outlined below. The requisite pentaene **4** was expected to arise *via* the sequential combination of phosphine oxide **5** and dioxinone phosphonate **6** with an appropriate aldehyde derived from enantiomerically pure, differentially protected triol **7** (Scheme 1).

Scheme 2[a]



[a]**Reagents**: a) NaH, pCH3OPhCH2Cl, THF, 25°C, 12h; b) *n*BuLi, -78°C, THF, 10min then $(CH_2O)_n$, -78°→ 25°C, 1h; c) LAH, THF, 0°C, 5h; d) NCS/DMS, CH_2Cl_2, 0°C 0.5h; e) Ph_2PLi, THF, -78°C , 1h then H_2O_2, 0°C, 5 min.

Preparation of **5** was accomplished by conversion of E-2-methyl-2-pentene-4-yn-1-ol to E, E allylic chloride **8** in 4 steps employing standard methodology (69% overall) as shown in Scheme 2.[9-11] Chloride **8** was then converted to the required phosphine oxide **5** in 50% yield by exposure of **8** to lithio diphenylphosphine and subsequent oxidation with H_2O_2 in CH_2Cl_2 at 0°C. Dioxinone phosphonate **6** was obtained in a single step (Eqn 1) from dioxinone **9**[12] *via* conversion to the lithium enolate with LDA and treatment with diethylchlorophosphite, followed by oxidation *in situ* (H_2O_2, CH_2Cl_2, 0°C) to afford a 60% yield of phosphonate **6**.[13]



(1)

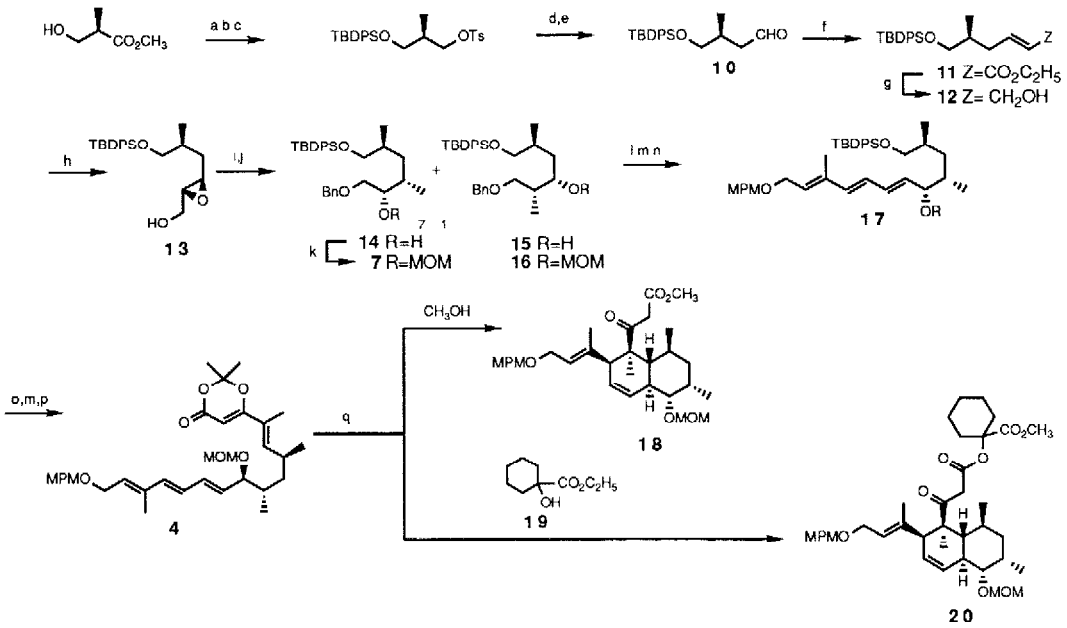
Construction of the enantiomerically pure triol **7** was initiated from (R)-(-)-methyl 3-hydroxy-2-methylpropionate which was converted in 5 steps using standard methods to aldehyde**10** in 73% overall yield (Scheme 3). Condensation of aldehyde **10** with the sodium anion of ethyl diethylphosphonoacetate afforded the expected E unsaturated ester **11** (97%) which provided allylic alcohol **12** upon reduction with DIBAL-H (95%). The two remaining stereogenic centers were installed *via* 3 step sequence involving catalytic asymmetric epoxidation[14] to afford epoxy alcohol **13** (88%, 88% de), followed by benzylation, and treatment of the protected epoxide with lithium dimethylcuprate in Et_2O at -45°C to afford a mixture (7:1) of diastereomeric alcohols **14** and **15** (86% combined from **13**).[15] Protection of the remaining alcohol as the methoxymethyl ether then furnished a readily separable mixture of the desired triol **7** (86%) and its regioisomer **16** (12%).[16]

Assembly of pentaene **4** from the three major subunits **5**-**7** was also readily accomplished (Scheme 3). Sequential catalytic debenzylation of **7** (~100%), Swern oxidation (90%),[17] and condensation of the resulting aldehyde with the lithium anion derived from **5** at -78°C in THF with added HMPA smoothly provided, as a single geometric isomer, the E,E,E triene **17** (86%). Repetition of the deprotection, oxidation, olefination sequence on **17** employing instead fluoride to cleave the silyl ether, and the lithium anion derived from **6** in THF with added HMPA delivered exclusively the required Z,E,E,E,E pentaene **4** (53% from **17**).[18]

With the key pentaene **4** in hand, we were in a position to test whether **4** fulfilled the crucial requirements of the intended tandem coupling/cycloaddition assembly of **2** and **3**: 1) that the thermally generated acyl ketene undergo efficient intermolecular capture by a suitable 3° alcohol (ultimately the required cyclohexene synthon **3**), and 2) that the subsequent cycloaddition proceed with high stereoselectivity creating the correct stereochemical relationships about the octahydronapthalene ring system.[19]

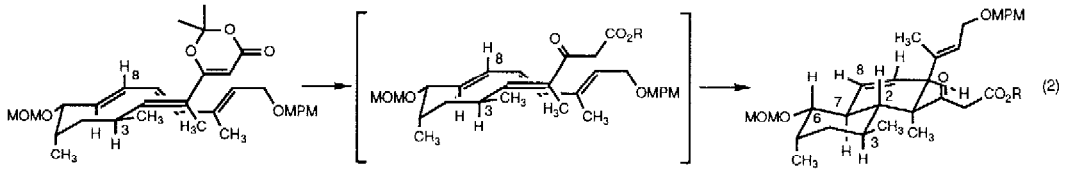
To test the essential feasibility of the coupling/cycloaddition, we first examined thermolysis of **4** at 110°C in the presence of excess methanol (~100 equiv), which afforded the desired decalin **18** in 54% yield along with 5% of uncharacterized diastereomeric cycloadduct(s)

Scheme 3[a]



[a]**Reagents** a) TBDPSCl, imidazole (2 equiv) , 25°C, 5h, b) DIBAL-H (2 equiv), THF, -78°C, 2h, c) TsCl, DMAP, Py, CH_2Cl_2, 25°C, 12h, d) KCN, EtOH-H_2O (1 1), Δ, 10h, e) DIBAL-H, THF, -78°→ 25°C, 1h, f) $C_2H_5O_2CCH_2P(O)(OC_2H_5)_2$, NaH, THF, -78°→ 25°C, 10h, g) DIBAL-H (2 equiv), THF, -78°C, 2h, h)Ti(OiPr)4 (catalytic), (-)DET (catalytic), tBuOOH, CH_2Cl_2, -20°C, 24h, i) NaH, $PhCH_2Br$, THF, 25°C, 1h, j) $(CH_3)_2CuLi$ (10 equiv), Et_2O, -45°C, 2h, k) CH_3OCH_2Cl, $EtN(iPr)_2$, THF, 25°C, 12h, l) H_2 (1 atm), Pd/C, EtOH, 25°C, 10h, m) $(COCl)_2$, DMSO, Et_3N, -78°C, 1h, n) **5**, *n*BuLi, THF-HMPA (2 1), -78°C, 1h, o) TBAF, THF, 25°C, 5h, p) **6**, *n*BuLi, THF-HMPA (2 1), -78°C, 2h, q) Δ (toluene , 110 °C (sealed tube), or xylenes, 130°C (sealed tube))

(Scheme 3) The stereochemistry of **18** was confirmed *via* 300 and 500 MHz NMR spectroscopy with appropriate decoupling [20] This result is consistent with the expectation that the cyclization would occur nearly exclusively through an endo-chair transition state in which the facial bias would be imparted by the C-3 substituent which preferentially occupies an equatorial orientation in the transition state so as to alleviate a non-bonded interaction with the C-8 proton [4c,5,6,21] We have also demonstrated the capture of a model 3° nucleophile in the form of hydroxy ester **19**, which afforded the related decalin **20** (~50%, unoptimized, >20 1 stereoselectivity) upon thermolysis of **4** at 130°C in xylenes in the presence of 1 equiv of **19**



Our studies have resulted in the development of an enantioselective route to key pentaene synthon **4** and the demonstration of the feasibility of a tandem coupling/cycloaddition methodolgy for the stereoselective preparation of octahydronaphthalene subunits for **1**. The following communication details our approach to cyclohexene **3**. Application of this methodology to the total synthesis of tetronolide **1** is currently under investigation.

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References and Notes:

(1) Tamioki, T.; Kasai, M.; Shirahata, K.; Tomita, F. *J. Antibiotics.* **1982**, *35*, 979.

(2) Waitz, J. A.; Horan, A. C.; Kalyanpur, M.; Lee, B. K.; Loebenberg, D.; Marquez, J. A.; Miller, G.; Patel, M. G. *J. Antibiotics* **1981**, *34*, 1101.

(3) Keller-Schierlein, W.; Muntwyler, R.; Pache, W.; Zahner, *H. Helv. Chim. Acta.* **1969**, *52*, 127.

(4) For leading references to prior work on chlorothricolide and kijanolide see: (a) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398. (b)Takeda, K.; Igharashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431. (c) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarity, K. J. *J. Org. Chem.* **1991**, *56*, 1192.

(5) Taken in part from the Ph. D. dissertation of Thomas E. Barta, University of Rochester, 1987.

(6) Boeckman, Jr., R. K.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421.

(7) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233.

(8) Ireland, R. E.; Varney, M. D. *J. Org. Chem* **1986**, *51*, 635.

(9) Corey, E. J.; Katzenellenbogen, N.; Gilman, N. W.; Roman, A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618.

(10) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

(11) All new substances exhibited satisfactory spectral (NMR, IR, MS) data and microanalytical or high resolution MS data.

(12) Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896.

(13) Boeckman, Jr., R. K.; Kamenecka, T. M.; Nelson, S. G.; Pruitt, J. P.; Barta, T. E. *Tetrahedron Lett.*, **1991**, *32*, 0000.

(14) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(15) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347.

(16) The minor isomers incurred in the asymmetric epoxidation and the subsequent epoxide opening were removed at the protected triol stage by chromatography(flash or prep HPLC) to give **7** as a homogeneous substance.

(17) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(18) The dioxinone phosphonate olefination proceeded in unsatisfactory yields in the absence of HMPA. Yields improved dramatically when a solution of the aldehyde in THF:HMPA(1:1, 1 M overall) was added to the lithiated phosphonate.

(19) Boeckman, Jr., R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286.

(20) Decoupling experiments verified that the C_2-C_7 coupling constant for the ring junction protons, and the C_6-C_7 coupling constant for the α-OMOM and adjacent ring junction protons were J=10.3 Hz and J=8.1 Hz respectively, consistent with *trans*-diaxial relationships between these protons and thus with *trans*- fused decalin **18** (Eqn 2).

(21) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am, Chem. Soc.*. **1987**, *109*, 1186.

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