ORGANIC LETTERS

2005
Vol. 7, No. 21
4589−4592

Synthesis of the C7–C15 *trans* Decalin Portion of the Natural Antibiotic Tetrodecamycin

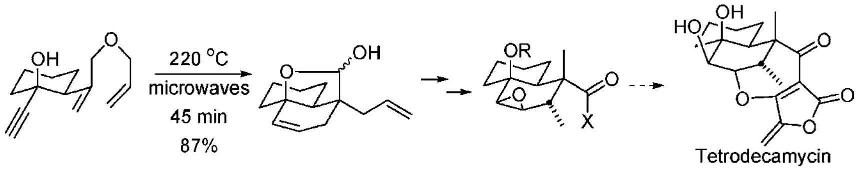
Jeffrey M. Warrington and Louis Barriault*

Department of Chemistry, 10 Marie Curie, University of Ottawa,
Ottawa, Ontario, Canada K1N 6N5

lbarriau@science.uottawa.ca

Received July 20, 2005

ABSTRACT



The tandem oxy-Cope/ene/Claisen rearrangement has been developed in our laboratory as a powerful method for rapid construction of complex Decalin cores. Herein, we describe the use of this method to generate the Decalin core of the natural antibiotic tetrodecamycin (1) bearing six contiguous stereocenters.

Tetrodecamycin (**1**) is a naturally occurring antibiotic isolated in 1994 from methanolic extracts of *Streptomyces nashvillensis* MJ885-mF8. It has shown distinct activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus anthracis*.[1] There has been considerable synthetic interest in this natural product, but to our knowledge no total synthesis has been published.[2]

In their studies on related structures, Paintner et al. demonstrated that the steric and conformational restraints imposed by the Decalin core are likely critical to biological function.[2b]

Our retrosynthetic analysis illustrated in Figure 1 shows disconnections of the C6−C2 acyl bond and C15−O macrocyclic ether ring. This reveals compact *trans* Decalin core **2** possessing six contiguous stereocenters including a quaternary carbon center[3] at C7 and a tetronic acid derived portion **3**. These two fragments could be connected together via aldol condensation between aldehyde **2a** and lithio tetronate **3a**[2d] or alternatively via palladium-catalyzed cross-coupling reaction between thioester **2b** and stannyl tetronate **3b** recently developed by Liebeskind.[4]

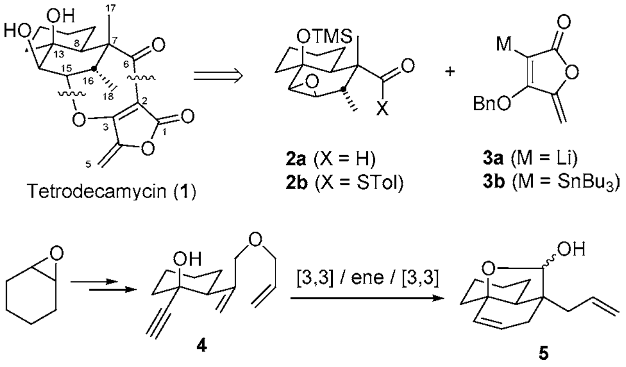


Figure 1. Retrosynthetic analysis of tetrodecamycin (**1**).

We envisioned that intermediate **2** could be rapidly constructed via cascade oxy-Cope/ene/Claisen rearrangement of allyl ether **4** to give the Decalin core **5**.[5] The latter could be readily prepared from commercially available cyclohexene oxide.

The synthesis commenced with epoxide opening[6] of cyclohexene oxide with isopropenylmagnesium bromide

---

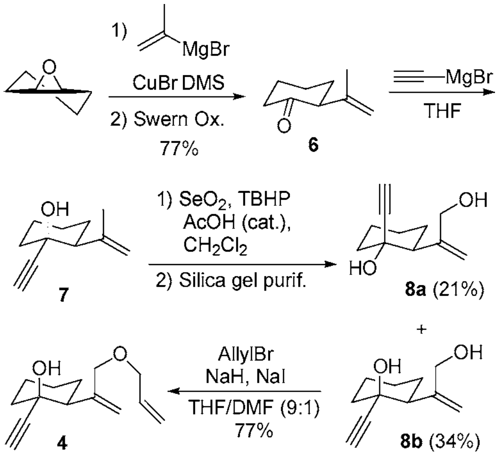
[1] (a) Tsuchida, T.; Iinuma, H.; Nishida, C.; Kinoshita, N.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1104. (b) Tsuchida, T.; Iinuma, H.; Sawa, R.; Takahashi, Y.; Nakamura, H.; Nakamura, K. T.; Sawa, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1110.

[2] (a) Paintner, F. F.; Bauschke, G. *Tetrahedron Lett.* **2003**, *44*, 2549 (b) Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Berns, C.; Heisig, P. *Bioorg. Med. Chem.* **2003**, *11*, 2823. (c) Paintner, F. F.; Allmendinger, L., Bauschke, G.; Polborn, K. *Synlett* **2002**, *8*, 1308. (d) Paintner, F. F.; Bauschke, G.; Kestel, M. *Tetrahedron Lett.* **2000**, *41*, 9977

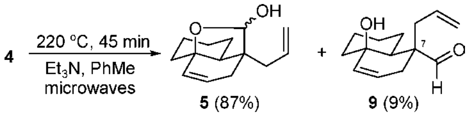
10.1021/ol051715f CCC: $30.25

followed by Swern oxidation[7] to afford ketone **6** in 77% overall yield (Scheme 1). Alkylation with ethynylmagnesium bromide provided **7** as a 1.5:1 ratio of inseparable stereomers. The allylic oxidation of **7** was accomplished with SeO_2 and *tert*-butyl hydroperoxide at room temperature over 2 days.[8] After purification, the desired diol **8b** was obtained in 34% yield over 2 steps (**8a** in 21% yield). Treatment of diol **8b** with allyl bromide and NaH in the presence NaI in a mixture of THF and DMF (9:1) gave the corresponding allyl ether **4** in 77% yield.

Scheme 1



Scheme 2



Microwave irradiation[9] of allyl ether **4** for 45 min in degassed toluene and triethylamine led to the desired *trans* Decalin **5** in 87% yield (Scheme 2). The mechanism of this transformation is depicted in Figure 2.

We had previously reported excellent diastereoselectivities for the tandem oxy-Cope/ene/Claisen reaction (>25:1 in most cases).[3] However, we now observed the formation of aldehyde **9** as a minor epimer at C7 in 9% yield. This is consistent with a *top* face Claisen rearrangement (**TS C**) of the resulting allyl enol ether conformer **C**. This result can be explained by planarization of the ring imposed by the unsaturation between C14 and C15, which diminishes the interaction between the allyl ether group and tertiary alcohol at the transition state.

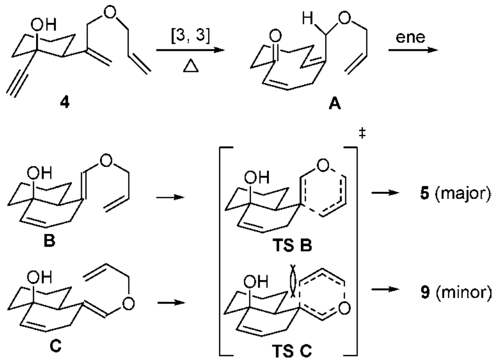
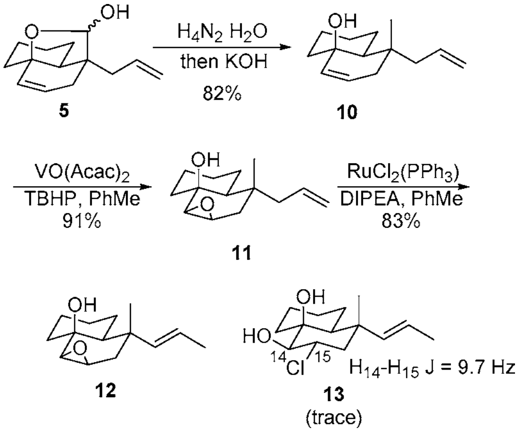


Figure 2. Mechanism of the oxy-Cope/ene/Claisen rearrangement.

With lactol **5** in hand, a complete reduction of the lactol moiety at C17 was carried out under the Wolff−Kishner conditions[10] to give the resulting tertiary alcohol **10** in 82% yield (Scheme 3). The allylic alcohol **10** was then subjected to the Sharpless epoxidation protocol[11] to furnish **11** in 91% yield over 2 steps as a single diastereomer. To gain access

Scheme 3



---

[3] For reviews on the synthesis of quaternary carbon centres, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *59*, 10105. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *110*, 42. (f) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (g) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

[4] (a) Liebeskind, L. S.; Strogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (b) Liebeskind, L. S.; Wittenberg, R.; Srogl, J.; Egi, M. *Org. Lett.* **2003**, *5*, 3033

[5] (a) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371. (b) Barriault, L.; Farand, J. A.; Denissova, I. *Heterocycles* **2004**, *62*, 735.

[6] Linstrumentelle, G.; Derguini-Boumechal, F.; Huynh, C. *Tetrahedron Lett.* **1979**, *20*, 1503.

[7] Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165.

[8] To produce the desired oxidation, 0.5−1.0 equiv of SeO_2 is required. See: (a) Ernet, T.; Haufe, G. *Synthesis* **1997**, 953. (b) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369. Cocatalysis with acid is often beneficial: (c) Julia, M.; Férézou, J. P. *Tetrahedron* **1990**, *46*, 475.

[9] For a review on microwaves in organic synthesis, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199. (d) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (e) Majetich, G.; Hichs, R. J. *J. Microwave Power Electromagnetic Energy* **1995**, *30*, 27.

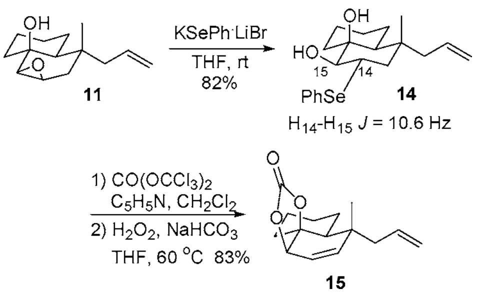
[10] (a) Kishner, N. J. *Russ. Phys. Chem. Soc.* **1911**, *43*, 582. (b) Wolff, L. *Ann.* **1912**, 394, 86. (c) Todd, D. *Org. React.* **1948**, *4*, 378. (d) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301.

to the aldehyde moiety present in **2a**, a migration of the terminal double bond was necessary. To this end, the exposure of **11** to a catalytic amount of $RuCl_2(PPh_3)_2$ and an excess Hunig's base at 150 °C in toluene overnight gave olefin **12** in 83% yield. Interestingly, trace amounts of **13** were noted when the reaction was carried out on large scale. Significantly, we noted that the epoxide had opened selectively at C15, and none of the regioisomeric C14 opening product was observed (Scheme 3).

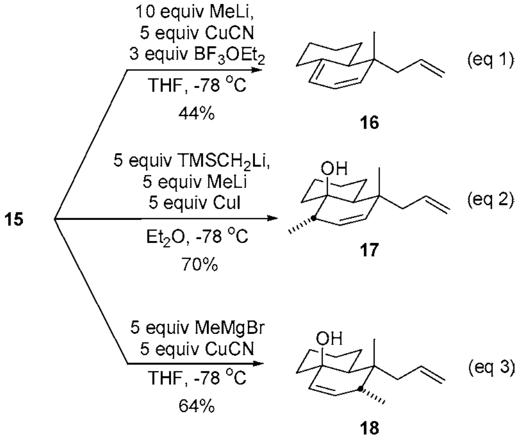
Realizing that this observation was pertinent to the current investigation, we now envisioned that the installation of the C18 methyl group could be possible via an epoxide opening−elimination−conjugate addition sequence.

Ring opening of the epoxide **11** with selenide produced *cis* diol **14** (83% yield) in a completely diastereoselective fashion (Scheme 4). Trapping the free diol as its carbonate derivative with triphosgene followed by an oxidative *syn* elimination of selenium afforded allylic carbonate **15** in 83% yield. From carbonate **15**, we proposed that the C18 methyl moiety could be installed via a copper-mediated S_N2' addition *anti* to the leaving carbonate group. This reaction revealed to be capricious in nature. Initial experiments employing copper(I) halides (e.g., CuI, CuBr) failed outright.

Scheme 4



Scheme 5



Interestingly, use of $BF_3{\cdot}Et_2O$ to activate the carbonate[12] resulted in complete decarbonylation, leaving behind 1,3-diene **16** in 44% yield (eq 1, Scheme 5). The Gillman cuprate derived from trimethylsilyl methyllithium led to the undesired direct S_N2 displacement product **17** in 70% yield (eq 2).[13] Finally, treatment of **15** with an excess of the cuprate reagent made from equal amounts of MeMgBr and CuCN[14] gave the desired allylic alcohol **18** in 64% yield possessing the correct carbon−carbon connectivity and stereochemistry (Figure 3).[15]

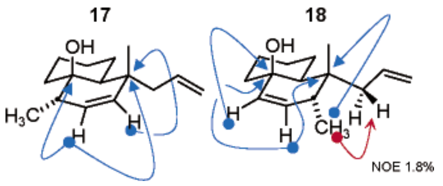
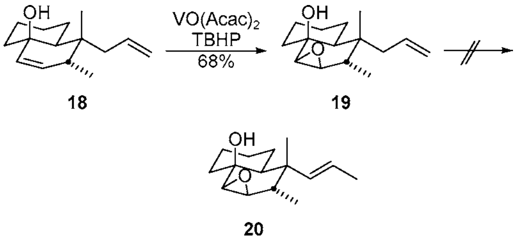


Figure 3. Sample correlations. Red = NOE, blue = HMBC.

Epoxidation of olefin **18** with the conditions applied before was possible; however, internal migration of the terminal olefin **19** to give **20** suffered from poor yields (Scheme 6).

Scheme 6



This problem was effectively circumvented by performing the epoxide opening−elimination−addition sequence after internalization of the double bond. (Scheme 7).

Epoxide **12** was easily converted to the corresponding selenide **21** (Scheme 7), which upon treatment with triphosgene followed by oxidative elimination afforded **22** in quantitative yield. An S_N2' addition of methyl cuprate and allylic epoxidation of the crude gave the desired internal olefin **20** in 61% yield over two steps.

Protection of the hindered tertiary alcohol was effected with LiHMDS and TMS-imidazole to yield **23**. Ozonolysis of this compound then led to the tetrodecamycin Decalin core **2a** in 71% yield. Oxidation of aldehyde **2a** with sodium chlorite afforded the corresponding carboxylic acid **24** in

---

(11) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

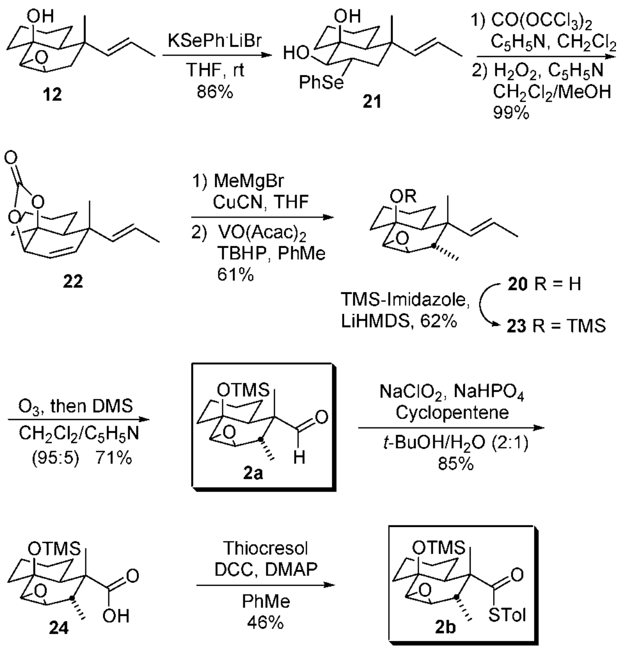
(12) Kang, S.-K.; Lee, D.-H.; Sim, H.-S.; Lim, J.-S. *Tetrahedron Lett.* **1993**, *34*, 91.

(13) (a) Gillman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. (b) Bertz, S. H.; Dabbagh, G.; Williams, L. M. *J. Org. Chem.* **1985**, *50*, 4414. (c) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

(14) Spino, C.; Tremblay, M.-C.; Godbout, C. *Org. Lett.* **2004**, *6*, 2801 and references therein.

(15) See Supporting Information for HMBC and NOESY of **17**, **18**, and **20**.

Scheme 7



85% yield. Finally, **24** was easily tranformed into the desired thioester **2b** in 46% yield by esterification with thiocresol, DCC, and DMAP.

In conclusion, we have demonstrated the utility of the tandem oxy-Cope/ene/Claisen reaction to rapidly construct the compact Decalin framework of natural antibiotic tetrodecamycin **2a** ands **2b** in 16 and 18 steps, respectively, from commercially available cyclohexene oxide. These intermediates possess the six contiguous stereocenters present in the natural product, with the correct relative stereochemistry at C7, C8, C13, C14, and C16. Investigation of the coupling reaction of the tetronic acid based moieties **3a**,**b** with Decalins **2a**,**b** and completion of the total synthesis of tetrodecamycin (**1**) is underway in our laboratory. These will be reported in due course.

Acknowledgment. We thank the Natural Scienceand Engineering Research Council of Canada (NSERC), PREA, Merck-Frosst Canada, Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca, Canada Foundation for Innovation, Ontario Innovation Trust, and the University of Ottawa for generous funding. J.M.W. thanks NSERC for a post-graduate scholarships (PGS-A and B).

Supporting Information Available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR for all new compounds, HMBC spectra of **17** and **18**, and NOESY spectra of **18** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051715F