ORGANIC LETTERS

2007
Vol. 9, No. 4
631−634

An Evans–Tishchenko–Ring-Closing Metathesis Approach to Medium-Ring Lactones

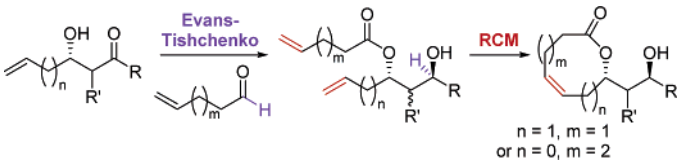
Jennifer I. Aird, Alison N. Hulme,* and John W. White

School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK

alison.hulme@ed.ac.uk

Received December 4, 2006

ABSTRACT

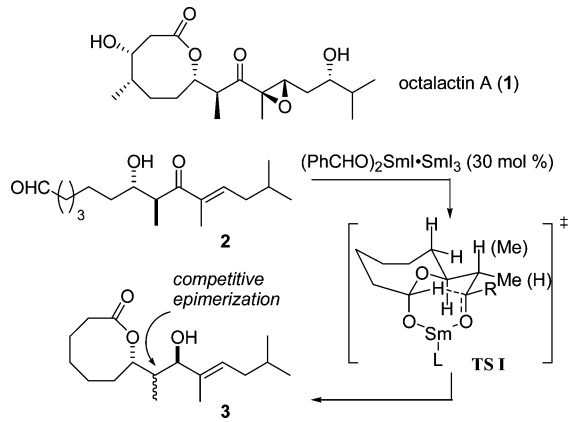


A new approach to the synthesis of medium-ring lactones is reported based on sequential Evans–Tishchenko and ring-closing metathesis (RCM) reactions. High diastereoselectivity (>95:5) is demonstrated in the Evans–Tishchenko reaction of unsaturated aldehydes with unsaturated *β*-hydroxy ketones, and conditions for the RCM cyclization of the resultant dienes have been optimized to give high yields of medium ring lactones. The synthetic utility of this sequence is demonstrated through generation of the fully functionalized core of octalactin A.

Medium-ring lactones (8- to 11-membered rings)[1] have attracted considerable interest due to the range of biological activity exhibited by natural products containing the lactone functionality. There are a relatively small number of methods used for closure of the lactone ring, the most popular traditionally being macrolactonization under high dilution conditions.[2] However, the yields obtained in the synthesis of medium-ring lactones using this method are rather unpredictable, and while a few notable examples exist where high-yielding macrolactonizations of medium rings have been carried out,[3] there is still considerable scope for the development of other approaches.[4]

We have previously reported a novel Evans−Tishchenko macrolactonization procedure in the synthesis of a model of the eight-membered lactone, marine polyketide octalactin A (**1**).[5] In this approach (Scheme 1) a *seco*-aldehyde precursor **2** was treated with a preformed samarium(III) catalyst prepared by mixing a THF solution of samarium diiodide and benzaldehyde to give the pinacol adduct $(PhCHO)_2SmI\cdot SmI_3$.[5] Evans−Tishchenko cyclization of the medium-ring lactone in the presence of 30 mol % of this catalyst was thought to be initiated by hemiacetal formation (**TS I**) followed by highly diastereoselective hydride transfer (>95:5) to form the *anti*-related hydroxylactone **3**. However, this

Scheme 1. Intramolecular Evans−Tishchenko Approach to the Octalactin A (**1**) Core[5]



(1) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777−2849.

(2) For a comprehensive review of macrolactonizations in the synthesis of natural products, see: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911−939.

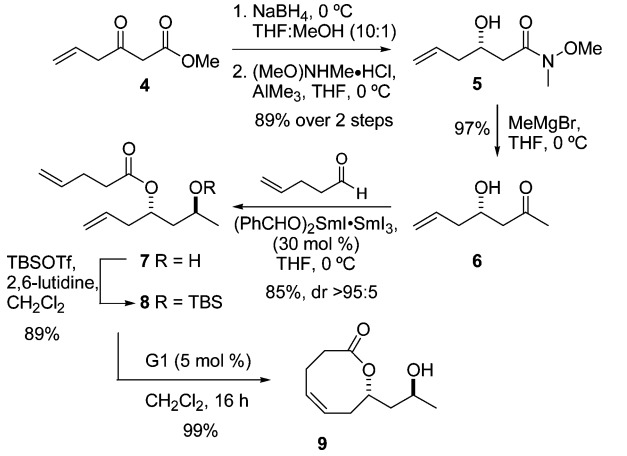
(3) (a) Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.; Ibuka, R. *Chem. Eur. J.* **2005**, *11*, 6601−6608. (b) Busek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511−5512.

10.1021/ol062932z CCC: $37.00
Published on Web 01/27/2007

approach to the octalactin core suffered from a number of deficiencies: First, competitive epimerization of the α-methyl group in the enone precursor was observed due to a relatively slow rate of cyclization. Second, the cyclized material was isolated in only a low yield, independent of the nature or mol % of catalyst used, the reaction time, or temperature. Finally, as an approach to a complex natural product such as octalactin A, the macrolactonization of a fully functionalized *seco*-aldehyde was not readily adaptable to a convergent strategy, making it rather unattractive. For these reasons, we sought to investigate an alternative approach to the synthesis of medium-ring lactones, such as that found in octalactin A.

Of particular interest were a limited number of recent reports of the application of ring-closing metathesis (RCM) to the synthesis of these challenging medium-ring lactones.[6,7,8] If the RCM reaction could be used in combination with the Evans−Tishchenko reaction as a fragment coupling strategy (rather than as the means of lactonization), we believed that we would be able to generate a highly diastereoselective and convergent approach to the synthesis of medium ring lactones. In order to test this hypothesis, we first required verification that the Evans−Tishchenko reaction could be successfully carried out using an unsaturated aldehyde. We thus set out to develop a very simple model of the octalactin core (Scheme 2). The required *β*-hydroxy ketone substrate was prepared in three steps by sodium borohydride reduction of 3-oxohex-5-enoate **4**,[9] conversion to the Weinreb amide **5** and reaction of the amide with methyl Grignard.[10] Treatment of *β*-hydroxy ketone **6** with a preformed samarium benzaldehyde pinacol adduct and pent-4-enal gave the *anti*-diol monoester **7** in high yield (85%) and with high diastereoselectivity (>95:5).[11] On this simple

Scheme 2. Eight-Membered Ring Lactone Synthesis Using an Evans−Tishchenko−RCM Strategy



model significant acyl migration was observed to form an undesired ester side product.[12] However, it was found that immediate protection of the free hydroxyl as the corresponding silyl ether prevented this. Ring closure of the protected ester **8**, using G1 catalyst [PhCH=$RuCl_2(PCy_3)_2$][13] at room temperature overnight, gave the unsaturated lactone **9** in quantitative yield. This simple lactone was found to be somewhat unstable in the presence of any traces of the ruthenium catalyst which remained after purification; in later studies, these problems were negated by removal of ruthenium from the reaction mixture through complexation with DMSO.[14]

With these promising results in hand, a new retrosynthesis of the octalactin core was envisaged (Scheme 3). In this alternative route, key intermediate **10** was targeted. Successful conversion of **10a** (P = TBS) to octalactin A has been reported by Busek et al., through directed epoxidation of the C(10)−C(11) double bond, oxidation of the C(9) alcohol to the corresponding ketone, and deprotection of the silyl ether,[3b] followed by hydrogenation of the oxecene double bond and oxidative cleavage of the PMB protecting group.[6b] We set out to synthesize the related compound **10b** (P = PMB)[15] using our combined Evans−Tishchenko−RCM approach. Retrosynthetic analysis of the metathesis precursor **11** led to the identification of two fragments: the C(1)−C(5) unsaturated aldehyde **12** and *β*-hydroxy ketone **13**, which in turn was readily identified as the product of a Horner−Wadsworth−Emmons (HWE) coupling of *β*-ketophosphonate **14** and C(11)−C(15) aldehyde **15**. Synthesis of the protected *β*-ketophosphonate **14** was facilitated by the

(4) For alternative approaches to the synthesis of medium ring lactones, see: (a) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194−2207. (b) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **2002**, *43*, 2815−2818. (c) Ohi, H.; Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1999**, 1757−1759. (d) Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1998**, 735−736. (e) Bermejo, A.; Tormo, J. R.; Cabedo, N.; Estornell, E.; Figadere, B.; Cortes, D. *J. Med. Chem.* **1998**, *41*, 5158−5166. (f) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682−4683.

(5) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245−8248.

(6) RCM approaches to the synthesis of 8-membered ring lactones: (a) Mohapatra, D. K.; Yellol, G. S. *Arkivoc* **2003** (ix), 21−33. (b) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181−184. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784.

(7) RCM approaches to the synthesis of 9-membered ring lactones: (a) Takahashi, T.; Watanabe, H.; Kitahara, T. *Heterocycles* **2002**, *58*, 99−104. (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81−88.

(8) RCM approaches to the synthesis of 10-membered ring lactones: (a) Kangani, C. O.; Bru1ckner, A. M.; Curran, D. P. *Org. Lett.* **2005**, *7*, 379−382. (b) Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 28−47. (c) Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 3356−3359. (d) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873−2875. (e) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synlett* **2003**, 1186−1188. (f) Liu, D.; Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005−3007. (g) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069.

(9) Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 133−140.

(10) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(11) A preformed Sm(III) catalyst was used to prevent any side reactions between the unsaturated aldehyde and Sm(II): Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3403.

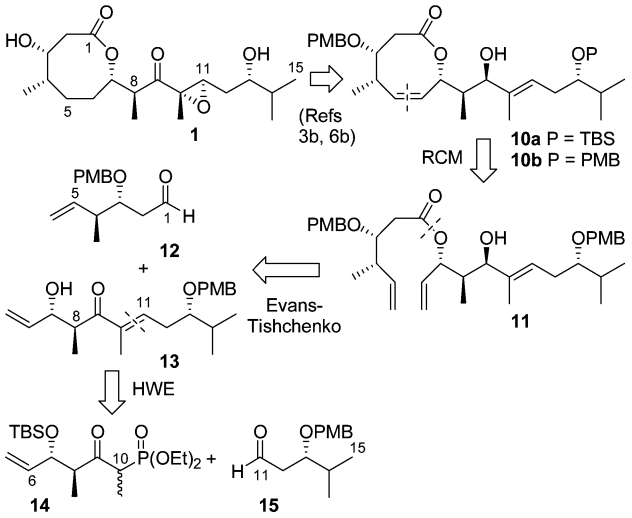
(12) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713−1723.

(13) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(14) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

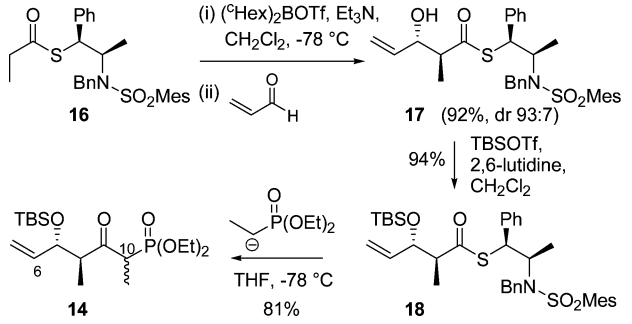
(15) It was anticipated that the differential protection of fragments **14** and **15** would allow a facile deprotection of the precursor to *β*-hydroxy ketone **13**, making **10b** a more attractive target.

Scheme 3. Retrosynthetic Analysis of Octalactin A (**1**)



use of our recently reported thiol equivalent of the Abiko−Masamune auxiliary (Scheme 4).[16] Dicyclohexylboron triflate

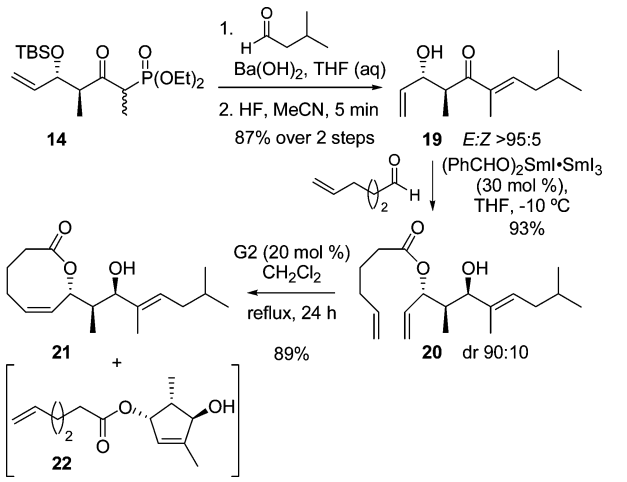
Scheme 4. Synthesis of Unsaturated β-Ketophosphonate **14**



mediated aldol reaction of propionate thioester **16** with acrolein gave an excellent yield of the desired *anti*-aldol adduct **17** in a 93:7 diastereomeric ratio (*anti*/*anti*). Silyl protection followed by facile displacement of the thiol auxiliary in **18** with the lithium anion of diethyl ethanephosphonate gave β-ketophosphonate **14** as a 4:1 ratio of diastereomers (66% overall yield from acylated auxiliary **16**).

Before investigating the use of functionalized aldehyde fragments **15** and **12**, β-ketophosphonate **14** was condensed with isovaleraldehyde under mild Horner−Wadsworth−Emmons conditions to furnish a protected enone (Scheme 5).[17] This protected enone was then treated with HF in acetonitrile to reveal β-hydroxy enone **19**. Evans−Tishchenko coupling to 5-hexenal gave the monoesterified *anti*-diol **20** in excellent yield (93%) and with good diastereoselectivity (90:10 *anti*/*syn*).[18] RCM of this more demanding

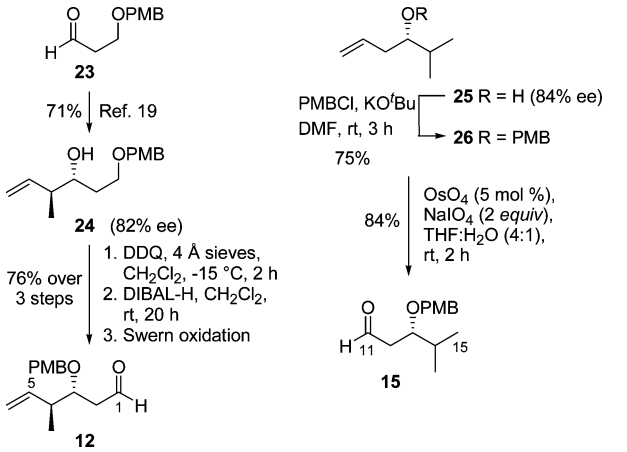
Scheme 5. Evans−Tishchenko RCM Strategy Using Unfunctionalized β-Hydroxy Enone **19**



unprotected substrate with G2 catalyst [PhCH═$RuCl_2$(PCy_3)-(H_2IMes)][19] allowed the isolation of unsaturated lactone **21**. Close examination of the ^{1}H NMR of the isolated material revealed a minor side product which was thought to result from competitive metathesis of the trisubstituted double bond (9:1 ratio, **21**:**22**). These promising results encouraged us to pursue this strategy for the synthesis of the fully functional octalactin precursor **10b**.

Synthesis of the C(1)−C(5) aldehyde **12** was achieved using a six-step sequence. Reaction of the (*E*)-crotylborane

Scheme 6. Synthesis of Aldehyde Fragments **15** and **12**



synthesized from freshly prepared (−)-Ipc_2BOMe with aldehyde **23**[20] gave homoallylic alcohol **24** as a single diastereomer (71% yield, 82% ee). PMB group transfer via the intermediate MPM acetal was effected through DDQ oxidation of **24** followed by regioselective DIBAL-H reduc-

(16) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219−4222.

(17) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774−776.

(18) Silyl protection of **20** was not required as no significant acyl migration was observed with this more sterically demanding substrate.

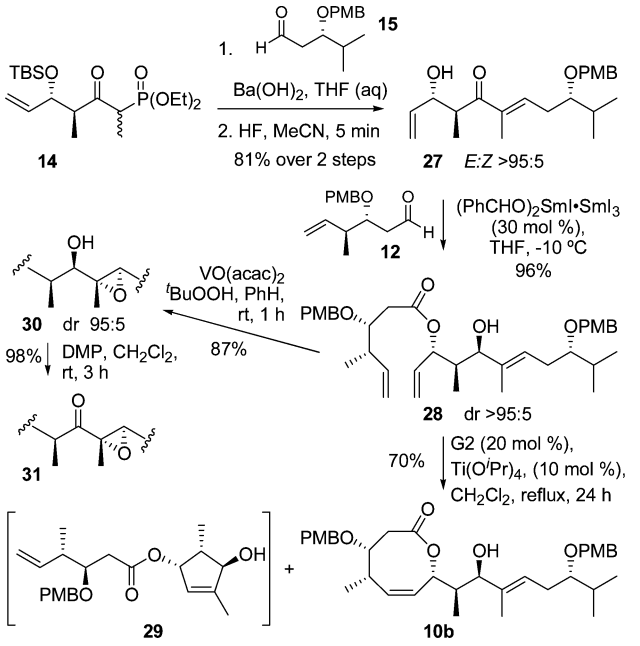
(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(20) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787−1798.

tion.[21] Finally, Swern oxidation gave aldehyde **12** (Scheme 6). For the synthesis of C(11)−C(15) aldehyde **15**, homoallylic alcohol **25** was generated through reaction of (−)-Ipc_2BOMe-derived allylborane with isobutyraldehyde (87% yield, 84% ee).[22] Protection of the secondary alcohol as its PMB ether (**26**), and one-pot oxidative cleavage of the double bond,[23] gave aldehyde **15**.

In order to investigate the synthesis of key intermediate **10b**, HWE coupling of protected β-ketophosphonate **14** with β-hydroxy aldehyde **15** was carried out (Scheme 7). The

Scheme 7. Synthesis of Key Intermediate **10b**



desired β-hydroxy enone **27** was isolated as a single double-bond isomer after HF deprotection of the silyl ether. Evans−Tishchenko fragment coupling of **27** was carried out in the presence of 2 equiv of the functionalized aldehyde **12**. Gratifyingly, under these conditions, ester **28** was isolated in 96% yield and as a single diastereomer. However, when this triene was subjected to the same RCM conditions as used on model substrate **20** [G2 (20 mol %), CH_2Cl_2, reflux, 24 h], a 1:1 mixture of the desired lactone **10b** and cyclopentene **29** was isolated in good overall yield (74%).[24] Use of the G1 catalyst, lower reaction temperatures, microwave conditions, alternative solvents such as toluene, or conversion of the C(9)−C(11) allylic alcohol to the corresponding epoxy alcohol **30**[25] or epoxy ketone **31** did not improve the yield of the desired cyclization, with essentially no identifiable products of ring closure isolated under any of these conditions. Finally, in an attempt to reduce any competitive chelation which might be hindering the desired cyclization process, a $Ti(O^iPr)_4$ cocatalyst was used along with the G2 catalyst.[26] Under these conditions, our target lactone **10b** was isolated as the sole reaction product in 70% yield.

In conclusion, we have shown that use of the Evans−Tishchenko reaction is a viable coupling strategy for a range of unsaturated partners and offers highly regioselective ester formation while at the same time conveying excellent diastereoselectivity. The RCM reaction, although it is subject to subtle steric and electronic influences, is again demonstrated as an efficient means of effecting medium ring closure. Overall, a combined Evans−Tishchenko−RCM approach provides a highly convergent strategy for the construction of medium rings; the longest linear sequence for the construction of lactone **10b** is merely eight steps.

Acknowledgment. We thank the EPSRC (DTA studentships to J.I.A. and J.W.W.) for financial support of this work and the Royal Society of Edinburgh/Scottish Executive (Research Support Fellowship to A.N.H.).

Supporting Information Available: Experimental procedures for the synthesis of compounds **14**, **19**−**21**, **12**, **15**, and **27**−**10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062932Z

(21) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2004.

(22) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404. (b) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223−226.

(23) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982−1992.

(24) Presumably introduction of the C(4) allylic methyl group in **28** (which is absent in **20**) renders the desired RCM relatively less favorable; hence, a shift from a 9:1 to 1:1 ratio of products occurs.

(25) The epoxide stereochemistry in **30** and **31** is assumed on the basis of literature precedent for epoxidation of the related lactones.

(26) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.