Pergamon

Tetrahedron Letters 40 (1999) 4267–4270

TETRAHEDRON
LETTERS

Eight Membered Ethers *via* Diene Metathesis: Synthetic Approach to Laureatin Natural Products

Simon D. Edwards,[a] Terence Lewis[b] and Richard J. K. Taylor[a]*

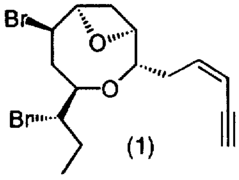
[a]Department of Chemistry, University of York, Heslington, York YO10 5DD, UK (Email: rjkt1@york.ac.uk)
[b]Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell RG42 6EY, UK

Received 11 March 1999; accepted 6 April 1999

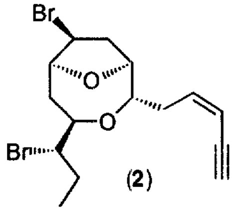
Abstract: *Ruthenium-mediated diene metathesis is applied to the synthesis of a range of oxocenes. The methodology is then utilised for the preparation of prelaureatin analogues. A successful synthesis of the 8-desalkyl analogue of prelaureatin in enantiomerically enriched form is described.*

The *Laurencia* red algae produce a range of bioactive medium ring bromoethers which have provided a significant challenge to synthetic organic chemists.[1] Laureatin (**1**) and isolaureatin (**2**) were isolated from *L. nipponica* by Irie *et al.* in 1968,[2] and the same group later determined their absolute configurations.[3] Insecticidal screening subsequently demonstrated that these compounds possess strong activity as mosquito larvicides (**1**: IC_{50} = 0.06 ppm: **2**: IC_{50} = 0.50 ppm).[4] Further studies resulted in the isolation of prelaureatin (**3**), the likely biosynthetic precursor of (**1**) and (**2**),[5] and of 3*E*-laureatin and 3*E*-isolaureatin.[6]

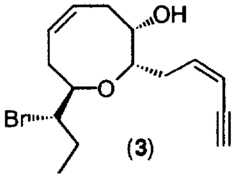
Much of the synthetic effort in the *Laurencia* area has been directed towards the biogenetically related lauthisan analogues exemplified by laurencin (**4**).[7] The laureatins are members of the less-well studied laurenan structural class. As part of our programme to synthesise medium ring natural products,[8] we envisaged preparing the laureatin family *via* prelaureatin (**3**), and obtaining this key intermediate by transition metal-mediated metathesis of a diene such as (**5**, P = protecting group).[9]



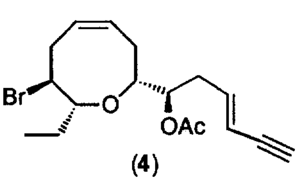
(1)



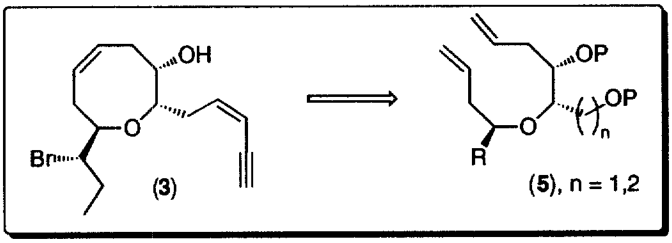
(2)



(3)



(4)



(3)

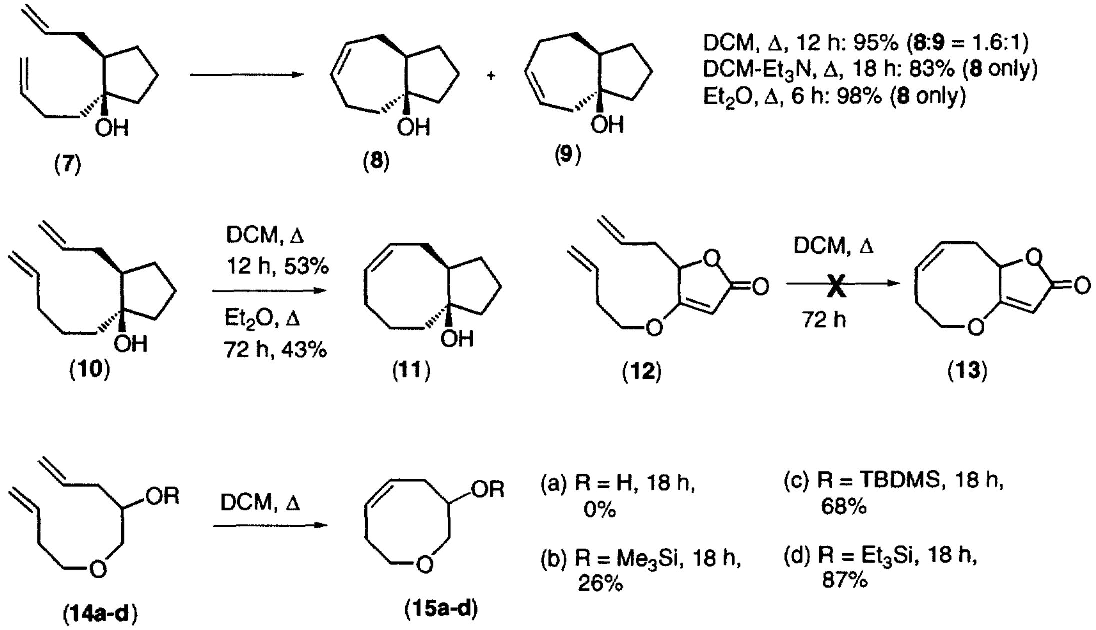
(5), n = 1,2

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00703-0

At the commencement of this study, there were few precedents[10] for the formation of medium rings *via* diene metathesis and so a series of model cyclisations was carried out to gauge the likely success of such an approach (Table).[11,12] In view of the normal difficulties encountered in seven and eight membered ring formation, initial studies were carried out on substrates containing pre-existing rings in order to provide entropic assistance to the cyclisation process. Thus, treatment of the annelated 1,8-diene (**7**) with Grubbs' catalyst (**6**)[13] in dichloromethane (DCM) at reflux gave a near quantitative yield of cyclopentenes (**8**) and (**9**). The formation of the unexpected product (**9**) was ascribed to acid catalysed isomerisation facilitated by the choice of solvent. Support for this hypothesis was provided by adding triethylamine to the dichloromethane reaction or changing the reaction solvent to diethyl ether: in these reactions the expected cycloalkene (**8**) was obtained in high yield as the sole product. With this success, the metathesis of the corresponding 1,9-diene (**10**) was attempted. We were delighted to observe that the expected annelated cyclooctene (**11**) was obtained in 53% unoptimised yield using dichloromethane as solvent without the occurrence of alkene isomerisation. In this case, the use of ether as solvent gave a lower yield and a slower conversion: dichloromethane was therefore employed for all of the remaining cyclisations to eight membered rings. Unfortunately, attempts to extend this procedure to the related butenolide (**12** → **13**) were unsuccessful.

Sufficiently emboldened by these model studies, we went on to study the cyclisation of the acyclic 1,9-dienes (**14**). Although the hydroxy-substituted example (**14a**) did not cyclise, the silylated analogues (**14b-d**) gave the required oxocenes (**15b-d**), with the triethylsilyloxy system (**15d**) being obtained in 87% yield. At the time these reactions were carried out they provided the first examples of non-annelated eight membered ring formation *via* diene metathesis, although other examples have been published subsequently.[14]

Table Metathesis reactions using 10 mol % $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**6**)

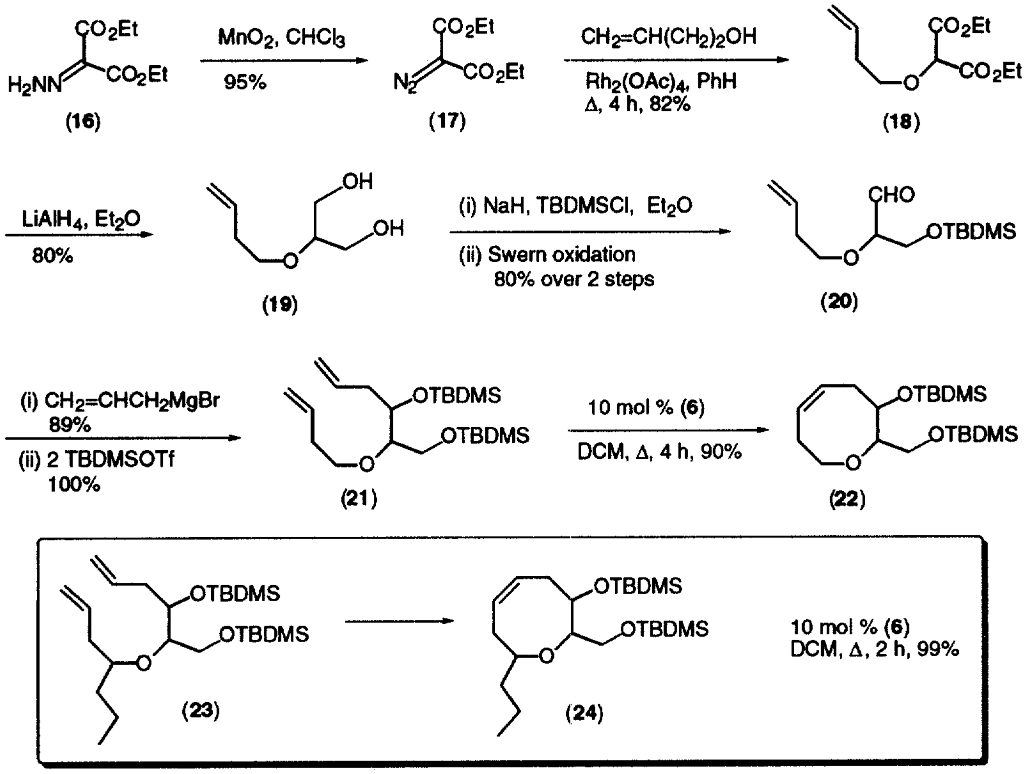


DCM, Δ, 12 h: 95% (**8**:**9** = 1.6:1)
DCM-Et_3N, Δ, 18 h: 83% (**8** only)
Et_2O, Δ, 6 h: 98% (**8** only)

(a) R = H, 18 h, 0%
(b) R = Me_3Si, 18 h, 26%
(c) R = TBDMS, 18 h, 68%
(d) R = Et_3Si, 18 h, 87%

Following these successful model studies, we went on to apply this methodology to the synthesis of more highly substituted oxocenes with a closer structural resemblance to the laureatins (Scheme 1). The most efficient route to the requisite 2-(butenyloxy)propane derivatives utilised the rhodium-mediated condensation of butenyl alcohol with diazo-compound (**17**).[15] Straightforward functional group modification then gave aldehyde (**20**) which was elaborated to give the metathesis precursor (**21**) in high yield. Treatment with Grubbs' catalyst (**6**) produced the disubstituted oxocene (**22**) as a 1:1 mixture of *syn* and *anti*-diastereoisomers. A similar sequence starting from hept-1-en-4-ol was employed to prepare diene (**23**) which underwent a near quantitative metathesis cyclisation to produce the propyl substituted oxocene (**24**) as a mixture of four diastereoisomers.

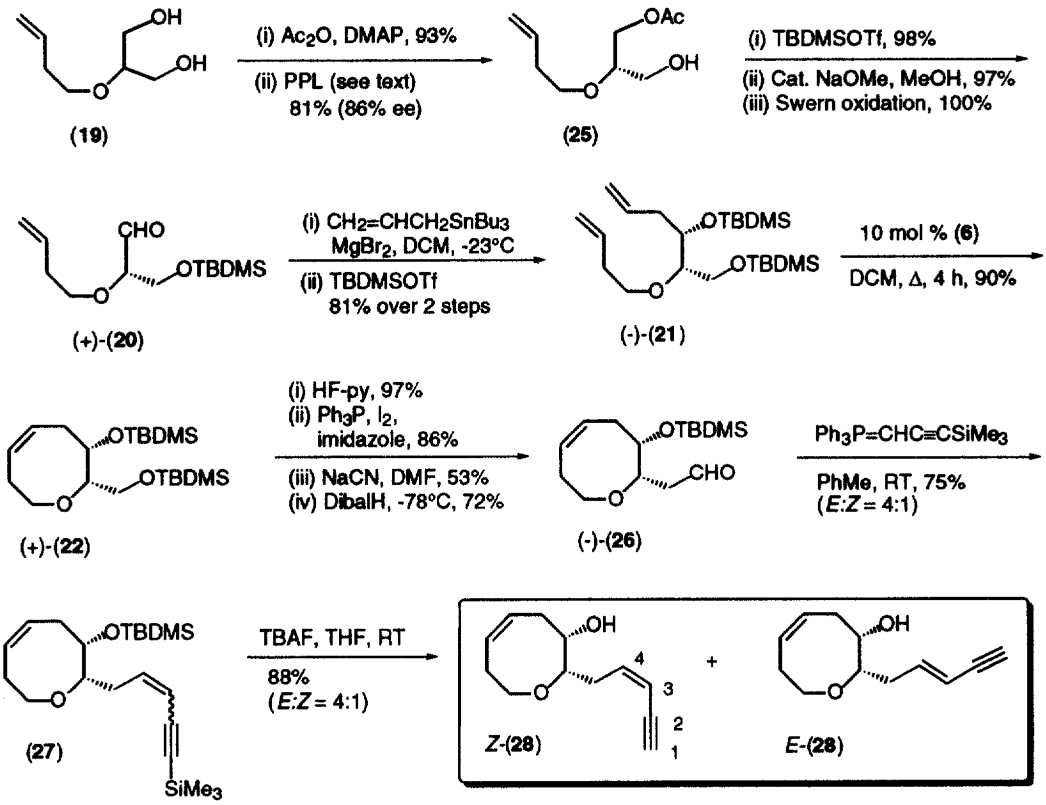
Scheme 1



The next objective was to devise a route to enantiomerically pure oxocenes. This was achieved by porcine pancreatic lipase (PPL)[16] treatment of the *meso*-diacetate derived from diol (**19**) as shown in Scheme 2. This protocol produced alcohol (**25**) in 81% yield{$[\alpha]_D$ +13.0 (c = 0.05, $CHCl_3$); 86% ee by Chiralcel OJ HPLC}. Functional group modification then produced aldehyde (+)-(**20**) which was allylated under chelation controlled conditions[17] using allyl-tributylstannane/$MgBr_2$ and then silylated to give adduct (-)-(**21**) as a single diastereoisomer in high yield. Metathesis as before gave oxocene (+)-(**22**) which was elaborated into aldehyde (-)-(**26**) using standard methodology. Wittig homologation[18] then produced enyne (**27**) as a 4:1 *E*:*Z* mixture. Desilylation followed by chromatographic separation gave the prelaureatin analogues *E*- and *Z*-(**28**) which lack the C-8 side chain. These compounds were fully characterised (including HRMS) and exhibited NMR spectroscopic data entirely consistent with those published for closely related natural products [*E*- (**28**): δ_C (67.8 MHz, $CDCl_3$) 76.6 (C-1), 82.8 (C-2), 111.1 (C-3), 143.3 (C-4); 3*E*-laureatin: δ_C (25.0 MHz, $CDCl_3$) 77.2 (C-1), 81.5 (C-2), 111.7 (C-3), 141.2 (C-4). *Z*-(**28**): δ_H (500 MHz, $CDCl_3$) 3.10 (1 H, d, *J* 2 Hz), 5.55 (1 H, br. d, *J* 11 Hz), 6.05 (1 H, dt, *J* 11, 8.5 Hz); prelaureatin[5] δ_H (400 MHz, $CDCl_3$) 3.16 (1 H, d, *J* 1 Hz), 5.58 (1 H, dq, *J* 11, 1 Hz), 6.09 (1 H, dt, *J* 11, 8 Hz)].

We are currently optimising and extending this methodology to prepare the laureatins and other analogues for biological screening.

Scheme 2



Acknowledgement We thank the EPSRC for a CASE studentship (S. E.).

References and Notes

1. Erickson, K. L. Ch. 4 in Marine Natural Products, Vol. 5, Ed. Scheur, P. J. Academic Press, NY, **1983**.
2. Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, 2091-2096; Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron Lett.* **1968**, 2735-2738; Irie, T.; Izawa, M.; Kurosawa, E. *Tetrahedron* **1970**, *26*, 851-870.
3. Kurosawa, E.; Furusaki, A.; Izawa, A.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 3857-3860.
4. Watanabe, K.; Umeda, K.; Miyakado, M. *Agric. Biol. Chem.* **1989**, *53*, 2513-2515.
5. Fukuzawa, A.; Takasugi, Y.; Murai, A. *Tetrahedron Lett.* **1991**, *32*, 5597-5598; Ishihara, J.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 737-740; Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai. A. *Tetrahedron* **1997**, *53*, 8371-8382.
6. Suzuki, M.; Kurosawa, E. *Bull. Chem. Soc. Jap.* **1987**, *60*, 3791-3792.
7. Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483-7498; Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958 and references therein.
8. Kling, M. R.; McNaughton-Smith, G. A.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1993**, 1593-1595; McNaughton-Smith, G. A.; Taylor, R. J. K. *Tetrahedron* **1996**, *52*, 2113-2124.
9. For a recent review see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 371-388.
10. Miller, S. J.; Kim, S-H.; Chen, Z-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109.
11. All new compounds were fully characterised by high field NMR spectroscopy and by elemental analysis and/or HRMS.
12. Cyclisation precursors (**7**), (**10**) and (**12**) were prepared by standard organometallic and alkylation methodology.
13. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
14. Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919-6920; Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548-7549.
15. Chouinard, P. M.; Bartlett, P. A. *J. Org. Chem.* **1961**, *26*, 2617-2618.
16. Didier, E.; Louginoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941-4958.
17. Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417-420.
18. Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025-1040.