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# A STRATEGY FOR THE ASYMMETRIC SYNTHESIS OF MEDIUM RING OXYGEN HETEROCYCLES: ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-OCTAHYDRODEACETYLDEBROMOLAURENCIN

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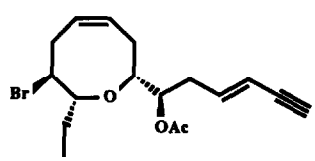
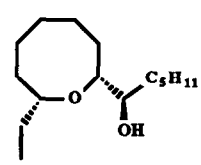
*Summary:* The asymmetric synthesis of the laurencin degradation product (**2**) by methylenation of the chiral heptanolide (**5**), conformationally controlled hydroboration of the enol ether (**6**), to give exclusively the *cis*-alcohol (**7**), and introduction of the pentyl side chain, demonstrates a new approach to the enantioselective synthesis of 2,8-disubstituted oxocanes, and confirms the absolute configuration of laurencin (**1**).

In recent years there has been an explosion of interest in biologically active natural products of marine origin. Many of the most interesting examples contain medium ring ethers,[1] as typified by the *Laurencia* metabolite laurencin (**1**).[2] Although, traditionally, the efficient synthesis of medium ring ethers has been an elusive goal,[3] several exciting solutions have emerged during the past two years.[4] The difficulty associated with these synthetic targets is illustrated in the only reported synthesis of (±)-laurencin.[5] In contrast, Overman and Thompson's recent synthesis of (-)-laurenyne illustrates the potential of new synthetic methodology.[6]

In this Letter we describe the first asymmetric synthesis of a saturated 2,8-disubstituted oxocane system as illustrated in the laurencin degradation product (**2**). Our approach is based on the previously undescribed enantioselective synthesis of 7-substituted heptanolides, followed by efficient lactone methylenation, and a remarkably highly diastereoselective hydroboration of the enol ether, employing medium ring conformational stereocontrol.

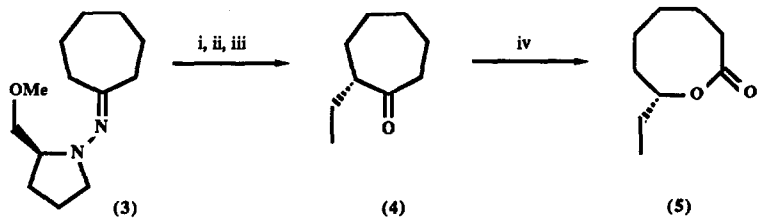



(1)




(2)

The chiral heptanolide (**5**) was obtained in high enantiomeric purity by the Baeyer-Villiger oxidation of 2(*R*)-ethylcycloheptanone (**4**). Parallel studies with side chain homologues of (**4**) have shown that high stereocontrol can be achieved in this oxidation without racemisation of the chiral ketone by using carefully controlled conditions employing $NaH_2PO_4$-buffered $CF_3CO_3H$ generated from >85% $H_2O_2$.[7] The chiral ketone (**4**) was obtained by a sequence involving diastereoselective low temperature alkylation of the SAMP-hydrazone (**3**),[8] followed by ozonolytic removal of the chiral auxiliary (Scheme 1).

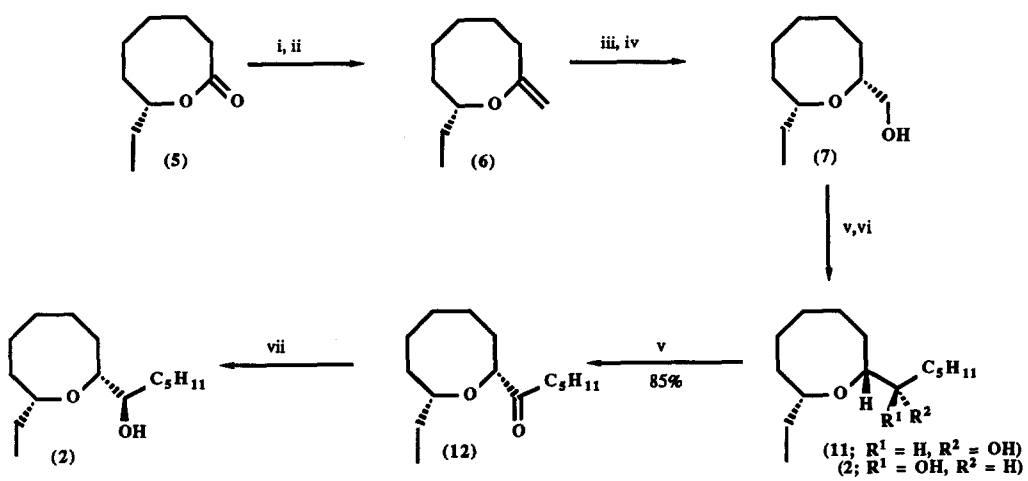



(3) (4) (5)

**SCHEME 1**

Reagents: (i) Lithium diisopropylamide, 0 °C, THF, 16 h; (ii) EtI, -95 °C, 3 h (87%); (iii) $O_3$, $CH_2Cl_2$, 15 min (68%); (iv) $CF_3CO_3H$, $NaH_2PO_4$, $CH_2Cl_2$, 0 °C to R.T. (70%).

Methylenation of the chiral lactone (**5**) with the Tebbe reagent[9] under modified conditions in which *N,N*-dimethylaminopyridine was used to generate the reactive alkylidene species gave a very labile enol ether (**6**). This was immediately hydroborated using the bulky borane reagent, diisoamylborane, to give, after oxidation, *exclusively* (analysis by capillary g.c.) the *cis*-isomer (**7**)[10] (Scheme 2) in good yield. By contrast hydroboration of racemic (**6**) with borane-THF complex yielded (**7**) and (**10**) in a ratio of 8:1. The minimum energy boat-chair conformation of (**6**), as calculated by Still's Macromodel[11] version of MM2, exposes the double bond to attack from a direction favouring the formation of *cis*-products, and this preference would be enhanced for bulky organoborane reagents. The evidence for the *cis*-product depends on three observations. The 3,5-dinitrobenzoate derived from the major alcohol (**7**) exhibits a positive n.O.e between the protons at C-2 and C-8 whereas the corresponding derivative of (**10**) shows no such effect. Equilibration in base of the aldehyde (**9**) derived from the minor alcohol favours the major (*cis*) compound (**8**) (8:1) at equilibrium (Scheme 3) in accord with the sense predicted by calculation of ground state minimum energies of the two aldehydes.[11] Finally, laurencin (**1**) has been been shown unambiguously by *X*-ray analysis[12] to have the *cis*-2,8-stereochemistry. It follows that the degradation product (**2**) has the same relative stereochemistry. Synthetic (**2**), derived from the major alcohol (**7**), is shown in the present work to be identical with an authentic sample.




(5) (6) (7) (2) (12)

**SCHEME 2**

Reagents: (i) $Cp_2Ti\begin{smallmatrix}CH_2\\Cl\end{smallmatrix}AlMe_2$, dimethylaminopyridine, THF, -40 °C to R.T.; (ii) 15% NaOH (aq.), -15 °C to R.T., 1 h; (iii) $Sia_2BH$, 0 °C, THF, 3 h; (iv) 3N NaOH, 30% $H_2O_2$ (44% from 5); (v) Pyridinium chlorochromate (PCC), 3Å molecular sieves, $CH_2Cl_2$, 1 h; (vi) $C_5H_{11}MgBr$, 0 °C, $Et_2O$ (52% from 7); (vii) $Li^sBu_3BH$, THF, - 78 °C (79%).

Completion of the synthesis of (2) required addition of pentylmagnesium bromide to the enantiomerically pure aldehyde (8). This gave a 1.5:1 mixture of (2) and (11). Attempts were made to improve the selectivity of formation of (2) over (11) by using magnesium bromide chelation control and organocuprate addition[13] to (8), but no significant improvement in selectivity was observed. However (2) was obtained with greater than 94% diastereoselectivity when the ketone (12) was reduced with L-Selectride.[14] The product {$[\alpha]_D$ + 19.6° (c = 1.52, $CHCl_3$, 21 °C} was identical in all respects (I.R., N.M.R., and t.l.c.)[10] with an authentic sample of (2) {$[\alpha]_D$ + 21.5° (c = 1.86, $CHCl_3$, 18 °C}.[2] The relative stereochemistry of (8) and (9) are respectively established as *cis* and *trans* as described above. The absolute stereochemistry of (8) is established by the extensive previous investigations of Enders.[8] The absolute configuration of laurencin was previously assigned by an empirical method[2] and by *X*-ray analysis.[12] The presently reported synthesis of (2) establishes its absolute configuration and independently confirms the absolute configuration of laurencin. This is significant because the absolute configuration assigned to laurenyne (a related *Laurencia* metabolite) by *X*-ray methods has recently had to be revised as a result of its total synthesis.[6]

In summary, the synthesis of (2) demonstrates the applicability of the method to the asymmetric synthesis of 2,8-disubstituted oxocanes and confirms the absolute configuration of laurencin.

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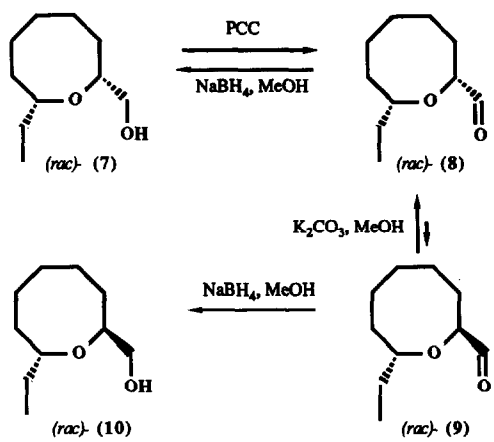


**SCHEME 3**

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7. This procedure was used to prepare 7(*R*)-pentylheptanolide, which, upon methanolysis and subsequent derivatisation of the resulting secondary alcohol as the Mosher ester, contained an e.e. of >94% (*R*)-enantiomer: A.B. Holmes, N.D. Pearson, and G.Slim, unpublished investigations.

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10. Selected spectroscopic data for (**2**): $^{1}H$ δ ($CDCl_3$) 0.88 (3H, t, *J* 7 Hz), 0.95 (3H, t, *J* 7.5 Hz), 1.25-1.78 (20H, m), 2.71 (1H, d, *J* 2 Hz), 3.27-3.42 (3H, m); $^{13}C$ δ ($CDCl_3$) 10.9, 14.1, 22.6, 23.4, 23.7, 25.4, 27.1, 29.2, 30.6, 32.0, 32.1, 33.3, 74.8, 82.2, 82.3.

Selected spectroscopic data for (**7**): $^{1}H$ δ ($CDCl_3$) 0.92 (3H, t, *J* 7.4 Hz), 1.29-1.81 (12H, m), 2.18 (1H, s), 3.34-3.50 (3H, m), 3.52-3.62 (1H, m); $^{13}C$ δ ($CDCl_3$) 10.8, 23.9, 23.9, 27.3, 29.6, 30.4, 33.1, 66.5, 80.3, 82.2; $[\alpha]_D$ (c 0.921, $CHCl_3$) + 7.9°.

All new compounds exhibited spectroscopic and analytical data consistent with the assigned structure.

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