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CONCISE ASYMMETRIC SYNTHESIS OF (5S, 6S)- AEGINETOLIDE AND (5S)- DIHYDROACTINIDIOLIDE

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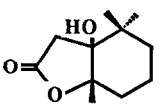
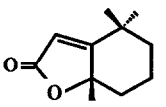
Abstract: An asymmetric deprotonation reaction allows for short syntheses of the lactones (5S, 6S)- Aeginetolide (1) and (5S)-Dihydroactinidiolide (2).

We recently showed that treatment of certain prochiral ketones with chiral lithium amide bases results in direct generation of chiral enolates which could then be transformed into a variety of optically active products.[1] Other recent reports also indicate the utility of chiral lithium amide bases for asymmetric transformation of both prochiral ketones,[2] and epoxides.[3] We now report the first application of this asymmetric approach, to the synthesis of (5S, 6S)- aeginetolide (1) and (5S)- dihydroactinidiolide (2),[4], which are naturally occuring lactones with interesting biological activities.[5]

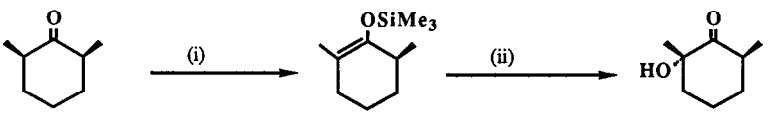


(1)

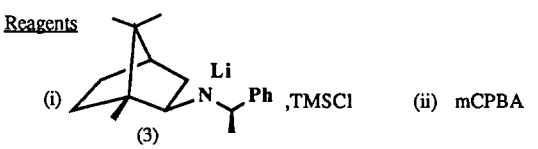


(2)

Treatment of cis -2,6-dimethylcyclohexanone with the chiral lithium amide base (3) at -78C to -30C overnight, followed by quenching with excess TMSCl/Et_3N gave the corresponding silyl enol ether (4). This volatile and labile product was purified by passing down a column of florisil and then directly reacted with mCPBA in petroleum ether to give hydroxyketone (5) in 65-76% yield overall, $[\alpha]_D$ +26.5 (c = 0.83, CH_2Cl_2), scheme 1.



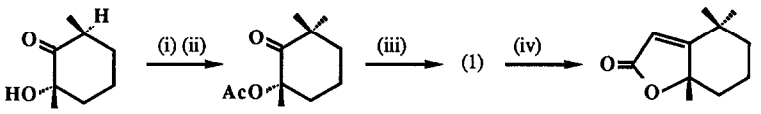
(4) (5)



(3)

Scheme 1

Examination of the H^1 nmr spectrum of (5) in the presence of $Eu(tfc)_3$ indicated an enantiomeric excess (ee) of 66%. This material was subsequently methylated using excess LDA/MeI, and then acetylated to give (6), $[\alpha]_D$-22.8 (c = 1.43, CH_2Cl_2), scheme 2.



(5) (6) (2)

Reagents (i) LDA, THF; MeI, HMPA, 25C (ii) Ac_2O, Et_3N, DMAP
(iii) LDA, THF, -78C (iv) $SOCl_2$

Scheme 2

Cyclisation of (6) was next accomplished using LDA at -78C (10 min), to give optically active aeginetolide (1),$[\alpha]_D$ +48.2 (c = 1.12, $CHCl_3$),[7] which was further reacted with $SOCl_2$ to afford dihydroactinidiolide (2), $[\alpha]_D$ +68.9 (c = 0.97, $CHCl_3$). Recrystallisation from ether/hexane gave (2) m.p. 69C, lit 67-68C[4]; $[\alpha]_D$ +118.9 (c = 0.56, $CHCl_3$), lit[4] [$\alpha]_D$ +120.9 (c = 1.00, $CHCl_3$) indicating an optical purity of ~98%.
In conclusion we have applied the asymmetric deprotonation method to the synthesis of optically active (5S)- dihydroactinidiolide in a very few steps, and in an overall yield of ~27%. Enantiomeric enrichment by recrystallisation then enables isolation of essentially optically pure material.

Aknowledgements

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2) M. B. Eleveld and H. Hogeveen,Tetrahedron Lett.,1986, 27, 631 ; R. Shirai, M. Tanaka, and K. Koga, J. Am. Chem. Soc., 1986, 108, 543.
3) M. Asami and H. Kirihara, Chemistry Lett., 1987, 389.
4) For previous syntheses of these compounds see K. Mori and Y. Nazakono,Tetrahedron, 1986, 42, 283, and references therein.
5) Dihydroactinidiolide possesses seed germination inhibitory activity, see K. L. Stevens and G. B. Merril, Experietia,1981,37, 1133; as well as being the queen recognition pheromone of the red imported fire ant, see J. R. Rocca, J. H. Tumlinson, B. M. Glancy, and C. S. Lofgren, Tetrahedron Lett., 1983,24, 1889.
6) tfc = 3-(trifluoromethylhydroxymethylene)- (-) -camphorato.
7) See G. M. Rubottom and H. D. Juve Jr., J. Org. Chem., 1983, 48, 422.

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