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Boc_2O Mediated Macrolactonisation : Formal Chemoenzymatic Synthesis of Macrolide Antibiotic (-) A26771B#

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Abstract : An efficient, stereocontrolled, formal chemoenzymatic synthesis of macrolide antibiotic A26771B (1) using the improved macrolactonisation reagent, Boc_2O- iPr_2 NEt/pyrrolidinopyridine(4-PP) is reported.

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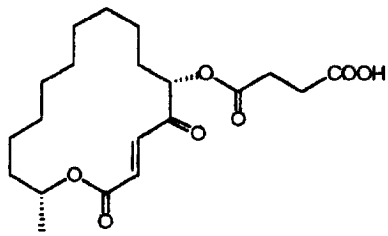
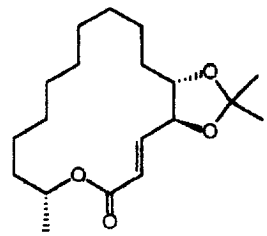
Key words : Macrolides;hydroxylation;enzyme reactions; lactonisation

The sixteen-membered macrolide antibiotic A26771B (**1**), isolated in 1977 from *penicillium turbatum* was found to be moderately active against gram-positive bacteria, mycoplasma and fungi [1]. Structurally, macrolide A26771B (**1**) possesses two chiral centres (5*S*,15*R*) and an α,ß-unsaturated double bond with a C-4 ketone. Structure elucidation of **1** and assignment of absolute stereochemistry was reported based on



A26771B (1)



2

biosynthetic and chemical degradation, NMR studies and Celmer's model [2,3]. The unique biological profile of A26771B (**1**) has generated tremendous interest among organic chemists and several racemic syntheses[4-9] and a few chiral syntheses [10-12] have been reported. Herein, we report the formal synthesis of the macrolide antibiotic A26771B (**1**) using Sharpless asymmetric dihydroxylation and enantioselective enzymatic acetylation techniques.

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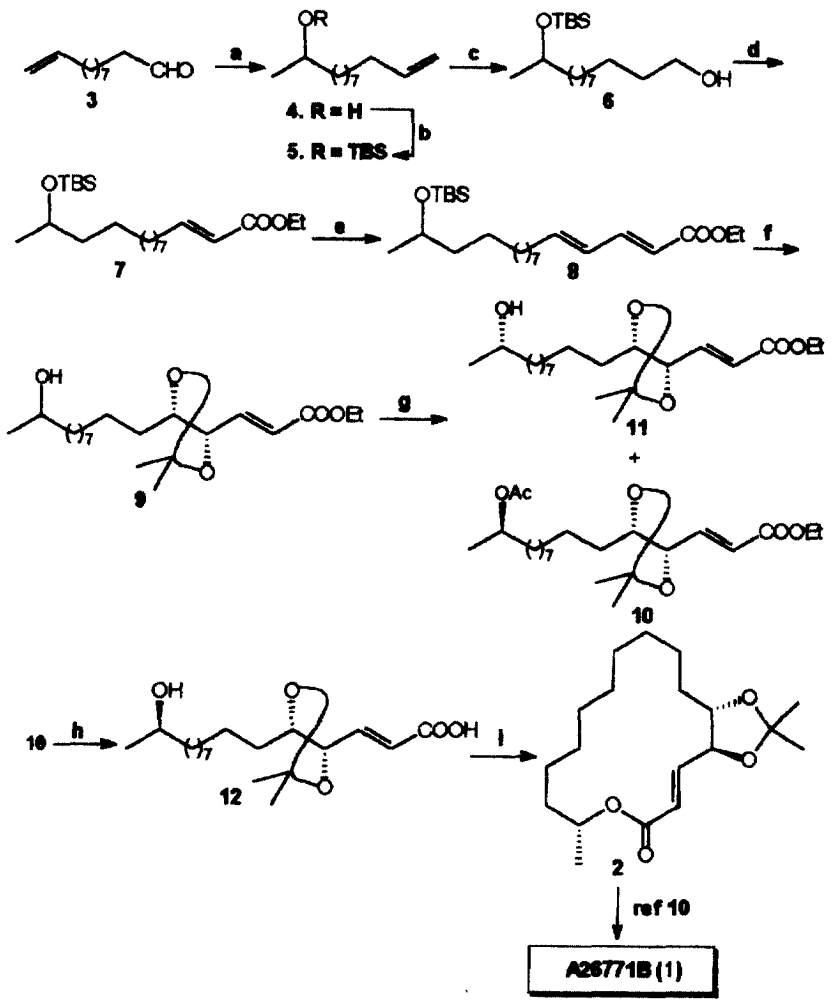
To begin with, our aim was to show the applicability of our recently developed di-*tert*-butyldicarbonate (Boc_2O) mediated macrolactonisation approach[13] for the construction of macrolide A26771B (1) which has so far, been synthesized generally by Yamaguchi macrolactonisation approach [14].

Scheme 1



Reagents : a. MeMgI, ether, 0°C, 2h, 81% b. TBSCl, imidazole, DCM, rt, 5h, 95% c. BH_3.DMS(2M),THF, NaOAc-30%H_2O_2, 0°C, 5h, 75% d. i) PCC-Celite, DCM, rt, 2h, 80% ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 6h, 85% e. DIBAL-H(1.0eq), toluene, -78°C, 2h then $Ph_3P{=}CHCO_2Et$, reflux, 4h, 76%(one pot). f. i) AD-mix-α, $MeSO_2NH_2$, ^tBuOH-H_2O (1:1), 0°C, 10h, ii)2,2-dimethoxypropane, acetone, 0.7eq PTSA, 80% g) CRL, isopropenylacetate, hexane, rt, 12h (30% conversion) h) CRL, phosphate buffer (0.05M), pH 7.2, rt, 26h, 69% i) Boc_2O-(i-Pr)$_2$NEt/pyrrolidino pyridine (4-PP), toluene, 90-95°C, 16h, 80%.

Accordingly, Grignard reaction of 10-undecenal (3) with MeMgI in ether at 0°C afforded the secondary alcohol **4** in 81% yield. Subsequent silyl protection of **4**, followed by hydroboration-oxidation of **5** furnished compound **6**. The primary hydroxyl group in **6** was oxidized to the aldehyde using PCC and treated with Ph_3P=CHCOOEt in benzene to afford the unsaturated ester **7**. The DIBAL-H reduction of **7** at - 78°C in toluene, followed by *in situ* Wittig reaction with Ph_3P=CHCOOEt (one-pot) under reflux conditions afforded the conjugated E,E - ester **8**[1]. Dihydroxylation of **8** at the electron-rich olefin by the Sharpless asymmetric dihydroxylation protocol[15] using AD-mix-α and methane sulphonamide in a 1:1 mixture of *t*-butanol/water afforded the crude diol which was subsequently protected as its acetonide with 2,2-dimethoxypropane in dry acetone and 0.7 eq. of PTSA to provide exclusively the hydroxy ester **9** (80 % for two steps).

As enzyme catalysed reactions are becoming routine tools for the resolution of racemic alcohols, the enantioselective acetylation of **9** was envisaged by using *Candida rugosa* lipase[16-20]. Accordingly, alcohol **9** was subjected to acetylation using *Candida rugosa* lipase (CRL, Sigma, type-7 , specific activity : 950 units/mg) and isopropenyl acetate in hexane at room temperature to yield the required (R)-acetate[1] **10** {30% conversion, e.e[$]. = 89.6% $[\alpha]_D^{25}$ -9.56 (c,0.62, $CHCl_3$)} and the unreacted (S)-alcohol **11**. The conventional chemical methods for ester hydrolysis using either LiOH or NaOH gave poor yields of the macrolactonisation precursor **12**. To circumvent this problem, the (R)-acetate **10** was subjected to enzymatic hydrolysis using CRL in phosphate buffer (0.05M, pH 7.2) at room temperature to furnish the hydroxy acid **12**.

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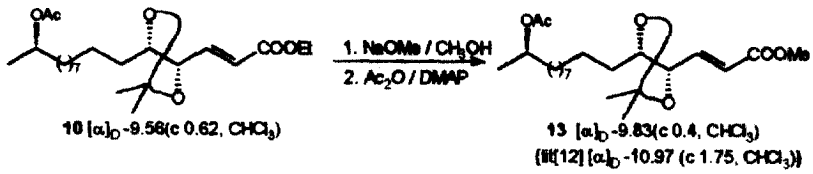
1 All the new compounds gave satisfactory spectal data. Spectral data of selected compounds

Compound **8** : IR (neat): 970, 1630, 1710, 2970 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 7.20 (m, 1H), 6.15-6.05 (m, 2H), 5.75 (d, 1H, J=15.6Hz), 4.15 (q, 2H, J=6.8Hz), 3.75 (m, 1H), 2.22-2.08 (m, 2H), 1.50-1.20 (m, 19H), 1.10(d, 3H, J=5.6Hz), 0.85 (s, 9H), 0.05 (s, 6H). **10** : $[\alpha]_D$ - 9.56 (c 0.62, $CHCl_3$). IR (neat) : 980 , 1720, 1735, 2985 cm^{-1}. ^1H NMR ($CDCl_3$, 200MHz): δ 6.85 (dd ,1H, J = 5.4, 16.0 Hz), 6.10 (d, 1H, J= 16.0 Hz), 4.85 (m,1H), 4.20 (q, 2H, J=6.6Hz), 4.10 (m,1H), 3.70 (m,1H), 2.02 (s,3H), 1.70-1.25 (m, 24H), 1.20 (d,3H,J=5.4Hz), 0.9 (t,3H,J=6.4Hz); EIMS: 397 (M^+ -CH_3); HRMS Calcd. for $C_{23}H_{40}O_6$: 397 .2590. Found : 397.2583.

$ The stereochemistry and enantiomeric excess of **10** was determined by converting it into the known reported derivative **13** and compared its optical rotation with the literature data [12].



10 $[\alpha]_D$ -9.56(c 0.62, $CHCl_3$)

13 $[\alpha]_D$ -9.83(c 0.4, $CHCl_3$)
{lit[12] $[\alpha]_D$ -10.97 (c 1.75, $CHCl_3$)}

The hydroxy acid **12** was subjected to newly developed macrolactonisation condition using Boc_2O-iPr_2NEt/pyrrolidinopyridine conditions in dry toluene at 90°C to provide the expected macrolide **2** in 80% yield. The spectral and physical data† of **2** were found to be in agreement with the data reported in the literature.[10,11] Since, conversion of **2** into antibiotic **1** is already reported in the literature [10,11], the synthesis of **2** formally constitutes the total synthesis of **1**.

In conclusion, an efficient, formal chemoenzymatic synthesis of macrolide antibiotic **1** was achieved in a relatively short reaction sequence and in good overall yield, starting from commercially available 10-undecenal (**3**). The synthesis employs novel macrolactonization conditions using Boc_2O-iPr_2NEt/4-PP without affecting other labile functionalities present in the molecule thereby also demonstrating the versatility and the efficiency of this newly developed process. Application of this new macrolactonisation condition to other complex macrolides is in progress.

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† **2**: mp: 68-69°C (lit[12] mp : 70-71°C); $[\alpha]_D$ + 6.79 (c 1.06 , $CHCl_3$) [lit[12] : $[\alpha]_D$ + 6.82 (c 1.75, $CHCl_3$)]; IR(neat) : 1665, 1715, 2965, 2985 cm^{-1} ; ^1H NMR ($CDCl_3$, 400MHz) : δ 6.88 (dd, 1H, J= 6.7, 15.6Hz), 6.13 (d,1H,J=15.6Hz), 5.05 (m,1H), 4.15 (dt,1H, J=1.02,8.3Hz), 3.75 (m,1H), 2.31(m,1H), 2.08(m, 1H), 1.80(m,1H), 1.65(s, 6H), 1.43(d, 3H, J= 5.6Hz), 1.38-1.18(m, 15H). ^{13}CNMR($CDCl_3$, 100MHz): δ 165.48, 144.23, 123.54, 80.73, 79.99, 71.10, 35.23, 30.97, 29.60, 27.77, 27.18, 27.11, 26.89, 26.50, 26.40, 24.74, 23.25, 20.42.EIMS: 324 (M+); HRMS Calcd. for $C_{19}H_{32}O_4$: 324.2301. Found : 324.2297.