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TETRAHEDRON: *ASYMMETRY*

A rapid formal synthesis of the macrolide (–)-A26771B

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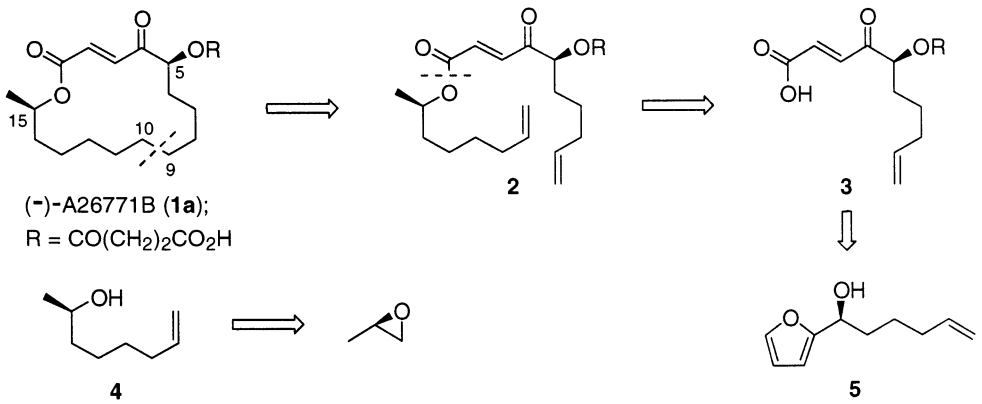
Abstract—(–)-A26771B, a novel 16-membered macrolide with antibiotic activity, has been formally synthesized. In the synthesis ruthenium catalyzed ring-closing olefin metathesis (RCM) was used as a key reaction to construct the lactone ring.

The macrolide antibiotic (–)-A26771B **1a**, produced by *Penicillium turbatum*,[1] possesses a 16-membered lactone which is a frequently found structural unit in numerous biologically active compounds such as tylonolide[2a] or epothilones.[2b] Due to its interesting biological activity, **1a** has attracted considerable synthetic effort and resulted in several successful approaches to the compound in both racemic[3] and optically active forms.[4] Most of the reported methods use intramolecular esterification as a key reaction to construct the lactone skeleton. Although the lactone forming reaction has been well established, preparation of the requisite starting material (i.e. hydroxyl carboxylic acid derivatives) has required long and tedious steps in many previous cases. Encouraged by the successful application of ring-closing metathesis (RCM) for the synthesis of medium-sized bioactive compounds,[5] we planned to synthesize **1a** based on the olefin metathesis strategy, which is described herein.

As outlined in Scheme 1, our strategy relies on the RCM of a linear tri-olefinic ester **2** to assemble the lactone skeleton of **1a**,[6] and coupling of the conjugated carboxylic acid **3** with the alcohol **4**. It was envisaged that the stereogenic center at C-(15) might be established by the ring opening of a chiral epoxide. By adapting Kobayashi's procedure[4b] the necessary carboxylic acid partner **3** would be accessible from oxidative ring cleavage of a furylcarbinol derivative **5**. Another asymmetric center at C-(5) would be provided by kinetic resolution of *rac*-**5**. It should be noted that the Grignard reagent 4-pentenylmagnesium bromide is employed here in the formation of both **4** and **5**, which makes this synthetic approach convenient and attractive.

Our synthesis is depicted in Scheme 2.[7] Addition of 4-pentenylmagnesium bromide to 2-furaldehyde afforded in excellent yield 2-furylcarbinol *rac*-**5**, which



Scheme 1.

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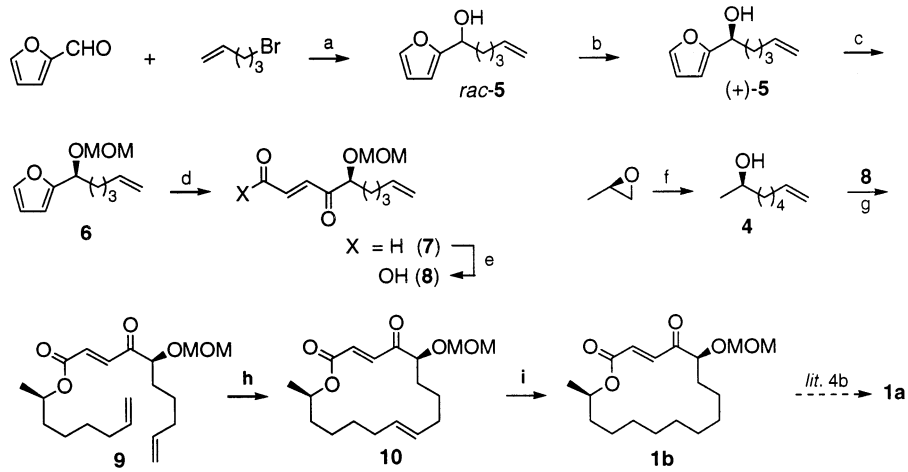

Scheme 2. *Reagents and conditions*: (a) Mg/THF, 99%; (b) $Ti(OiPr)_4$ (0.2 equiv.), D-(−)-DIPT (0.2 equiv.), *t*-BuOOH (0.55 equiv.), −20°C, 12 h, 42% based on *rac*-**5**; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 94%; (d) NBS (1.3 equiv.), $NaHCO_3$ (2 equiv.), furan (3 equiv.), pyridine, 55%; (e) $NaClO_2$ (3 equiv.), $Me_2C{=}CHMe$ (10 equiv.), 100%; (f) 4-pentenylmagnesium bromide, CuBr (0.1 equiv.), 94%; (g) 2,4,6-$Cl_3C_6H_2COCl$ (3 equiv.), NEt_3 (3 equiv.) DMAP (2 equiv.), 52%; (h) $Cl_2(PCy_3)_2Ru{=}CHPh$ (12 mol%), CH_2Cl_2, rt, 16 h, 76%; (i) H_2/PtO_2, EtOAc, 30 min, 25°C, 55%.

was subsequently resolved into the optically active form (+)-**5** under the Sharpless conditions by treatment with 0.55 equiv. of *t*-BuOOH in the presence of 0.2 equiv. each of $Ti(OiPr)_4$ and D-(−)-DIPT in CH_2Cl_2.[8] The more slowly reacting starting material, (+)-**5**, was isolated by silica chromatography in 42% yield. The enantiomeric excess (+)-**5** was found to be >95% by ^1H NMR spectroscopy of the corresponding Mosher ester.[9] After protection of (*S*)-**5** as its methoxymethyl ether **6**, oxidative ring cleavage of the furan derivative was next performed according to the Kobayashi's protocol,[10] in which NBS (1.3 equiv.) was used in combination with furan and pyridine to afford 4-oxo-2-enal **7**. Oxidation of **7** to the corresponding conjugated acid **8** was carried out with sodium chlorite in quantitative yield. Homochiral secondary alcohol **4** was readily obtained in 94% yield by ring-opening reaction of a commercially available (*R*)-propylene oxide. Among several other coupling reagents examined, 2,4,6-trichlorobenzoyl chloride turned out most efficient for esterification of **8** with **4**, and the linear trialkenyl ester **9** was obtained in 52% yield under Yamaguchi's conditions.[11]

Ring closure was carried out using the well-established RCM protocol.[12] At low concentration (0.005 M in CH_2Cl_2), Grubbs' catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (12 mol%) was added in three portions over 16 h at room temperature and the (2*E*,9*E*)-isomeric lactone **10** was isolated in 76% yield. Selective reduction of the isolated (9*E*)-double bond of **10** in preference to the conjugated (2*E*)-bond was achieved by hydrogenation in the presence of a PtO_2 catalyst in ethyl acetate over 30 min at room temperature to afford **1b** in a 55% yield.[13] Surprisingly, Wilkinson's rhodium complex $RhCl(PPh_3)_3$ catalyzed hydrogenation of the conjugated double bond exclusively, and the isolated olefinic bond of **10** did not react. Spectral data (^1H, ^{13}C NMR, and IR) for the synthesized lactone **1b** are in full agreement with that reported by Kobayashi et al.: ($[\alpha]_D^{25}$ −54.4 (*c* 0.25, $CHCl_3$); lit.[4e] $[\alpha]_D^{27}$ −49.3 (*c* 0.28, $CHCl_3$)).[14]

In summary, a concise formal synthesis of an antibiotic (−)-A26771B has been achieved by the use of ruthenium catalyzed RCM to construct the required 16-membered lactone skeleton. The synthetic approach presented is highly convergent and convenient, and is easily amenable to the synthesis of structural variants of (−)-A26771B.

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14. Transformation of **1b** to (–)-A26771B (**1a**) has been reported in previous literature.[4b]