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SYNTHESIS OF THE BOTTOM HALF OF CHLOROTHRICOLIDE

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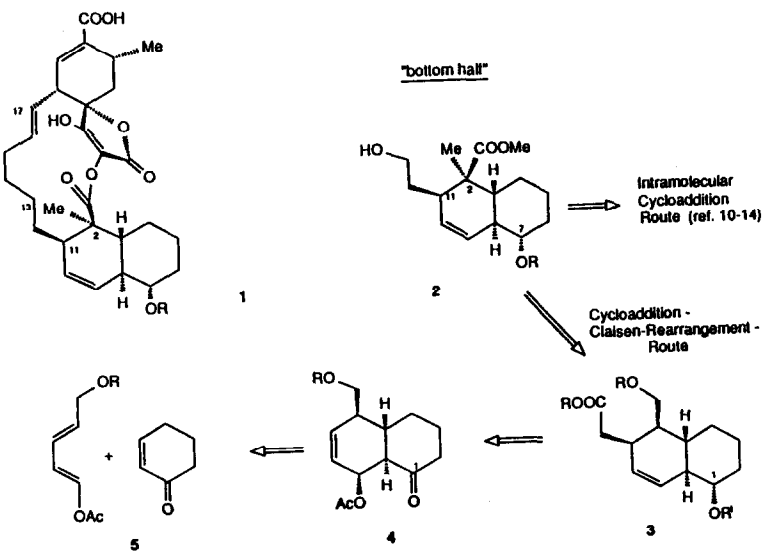
Abstract: Diels-Alder reaction of 1-acetoxy-pentadienol derivative **5** with cyclohexenone afforded cycloadduct **6** which gave with base the trans-octahydronaphthalene skeleton **4**. Diastereoselective reduction of the keto group and then Claisen-Ireland rearrangement furnished octahydronaphthalene **3** which was readily transformed into the target molecule **2**.

Chlorothricin[1] and the related antibiotics kijanimycin[2] and tetrocarcin[3] belong to a structurally new type of macrolides. The central moieties of the aglycon portion are a cyclohexene-spirotetronate and a trans-octahydronaphthalene unit. Both these moieties are part of a 14- or 13-membered macrocycle, respectively, which carry oligosaccharide residues. The aglycon portions, which are called chlorothricolide[1] (Scheme 1, compound **1**), kijanolide[2], and tetronolide[3], respectively, are structurally very similar.

Scheme 1



Obviously, retrosynthesis of chlorothricolide (**1**) suggests a disconnection of one of the carbon bonds between C-13 and C-17 and of the ester bond providing the two essential moieties which were-

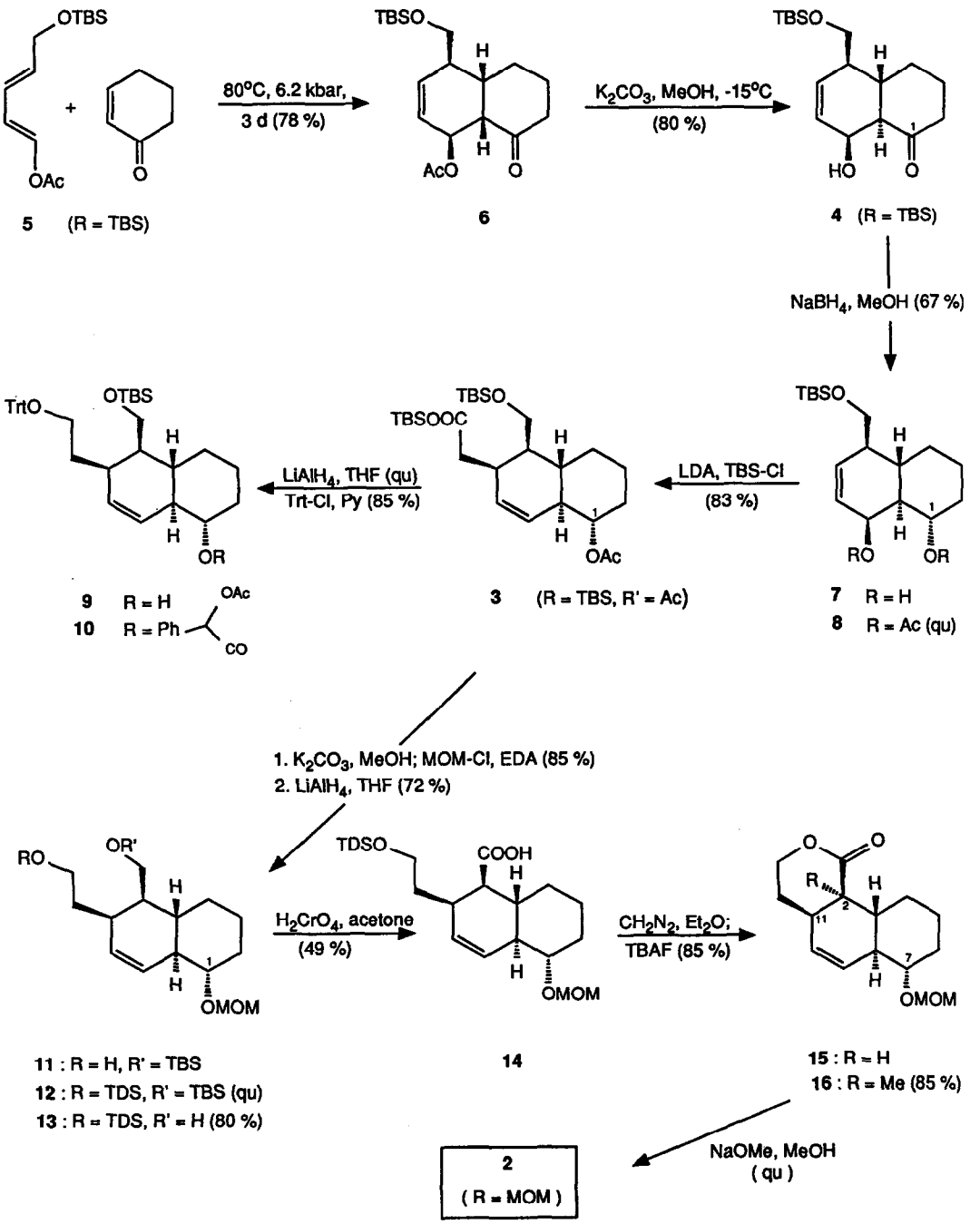
designated by Ireland and coworkers[4] as "top half" and "bottom half". Recent interest in the synthesis of chlorothricin, which is active against Gram positive bacteria as a noncompetitive inhibitor of pyruvate carboxylase[5], resulted in approaches to the synthesis of the top half[4-8], of the bottom half[4,7,9,12], and of a model chlorothricolide[4,13]. Mainly intramolecular Diels-Alder reaction was employed for constructing different homologs of the octahydronaphthalene moiety of the bottom half **2**[9-13]. We demonstrate the efficiency of a simple Diels-Alder approach for generating the octahydronaphthalene skeleton with the required relative stereochemistry and a Claisen-Ireland rearrangement[14] for introducing the C-2 alkyl side chain and concomitantly shifting the double bond in 9,10-position of **2**[7]. Thus, as outlined in the retrosynthesis (Scheme 1) compounds **3** and **4** are decisive intermediates.

Diene **5** (Scheme 2) was obtained from the readily available 1-acetoxy-1,3-pentadien-5-ol[15] by O-silylation with tert-butyldimethylsilyl chloride (TBS-Cl). Diels-Alder reaction with 2-cyclohexenone under high pressure afforded mainly the exo-adduct **6** (exo:endo:regioisomers = 18:1:1) which was separated by chromatography. Treatment with K_2CO_3/MeOH at -15°C led to deacetylation and clean epimerization furnishing the desired trans-octahydronaphthalene intermediate **4**[16]. Direct reduction of this compound with $NaBH_4$/MeOH gave in a 9:1 ratio preferentially the diol **7** with the desired relative stereochemistry of the new hydroxy group. The di-O-acetyl derivative **8** thereof, whose ^{1}H-NMR data confirm the structural assignments[16], gave on treatment with LDA/TBS-Cl the expected mono-Claisen-Ireland rearrangement product **3**. Thus, the substituted octahydronaphthalene skeleton with the required relative stereochemistry was readily obtained in five highyielding steps. Reduction of compound **3** with $LiAlH_4$ and then selective tritylation of the primary hydroxylic group afforded intermediate **9** with a free secondary hydroxylic group. Treatment with optically active mandeloyl chloride in presence of pyridine furnished compound **10** which could be used for the resolution of this material[18].

The final execution of the bottom half **2** synthesis required the modification of the carbon side chains in intermediate **3** and finally the introduction of the missing methyl group. To this aim, base catalyzed methanolysis of compound **3**, protection of the secondary hydroxylic group with methoxymethyl chloride (MOM-Cl) in presence of Hünig's base (EDA), and then ester group reduction with $LiAlH_4$ in THF was performed yielding compound **11**. Protection of the hydroxyethyl side chain with tert-butyl-diphenylsilyl chloride (TDS-Cl) in presence of imidazole furnished compound **12** in quantitative yield. Selective removal of the TBS protective group in presence of the TDS protective group with pyridinium p-toluenesulfonate according to Prakash et al.[18] afforded the desired product **13**. Jones oxidation (H_2CrO_4 in acetone) gave carboxylic acid **14** which was treated with diazomethane in ether and then with tetra-butylammonium fluoride (TBAF) to furnish lactone **15** (84 %). Deprotonation with LDA in THF and then reaction with methyl iodide provided diastereoselectively the desired C-2 methylated product **16**[16] in 85% yield. Lactone opening with sodium methoxide in methanol led to the desired compound **2**[16] which was identical in all relevant ^{1}H-NMR data with a similar compound synthesized by Roush et al.[9b], thus concluding an efficient synthesis of the chlorothricolide bottom half.

Enantioselectivity for the cycloaddition with the help of chiral auxiliaries and extensions to the synthesis of the bottom halfs of kijanolide an tretronolide, respectively, are under investigation.

Scheme 2[a]



[a] Besides compounds **9** and **10**, all compounds are racemates.

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16. ^{1}H-NMR data (250 MHz, $CDCl_3$) of **4**: δ = 5.73 (ddd, 1H, H-6, $J_{6,7}$ = 10.4, $J_{5,6} \approx J_{6,8} \approx$ 1.5 Hz), 5.66 (ddd, 1H, H-7, $J_{6,7}$ = 10.4, $J_{7,8}$ = 4.5, $J_{5,7}$ = 2.2 Hz), 4.45 (ddd, 1H, H-8, $J_{8,8a}$ = 8.8, $J_{7,8}$ = 4.5, $J_{6,8}$ = 1.9 Hz), 3.8-3.6 (m, 2H, CH_2-OTBS), 3.22 (sb, 1H, OH), 2.6-1.5 (m, 9H, 2 H-2, 2 H-3, 2 H-4, H-4a, H-5, H-8a), 0.87 (s, 9H, ^{t}Bu), 0.04, 0.03 (2s, 6H, $SiMe_2$).- **8**: δ = 5.89 (ddd, 1H, H-6, $J_{5,6}$ = 5.2, $J_{6,7}$ = 10.1, $J_{6,8}$ = 1.4 Hz), 5.53 (ddd, 1H, H-7, $J_{5,7}$ = 1.0, $J_{6,7}$ = 10.1, $J_{7,8}$ = 2.7 Hz), 5.31 (dddd, 1H, H-8, $J_{5,8}$ = 1.3, $J_{6,8}$ = 1.4, $J_{7,8}$ = 2.7, $J_{8,8a}$ = 7.6 Hz), 4.64 (ddd, 1H, H-1, $J_{1,2}$ = 4.0, $J_{1,2'}$ = $J_{1,8a}$ = 10.4 Hz), 3.69 (mc, 2H, CH_2OTBS), 2.30-1.20 (m, 8H, 2 H-2, 2 H-3, 2 H-4, H-4a, H-5), 2.13 (ddd, 1H, H-8a, $J_{1,8a}$ = 10.4, $J_{8,8a}$ = 7.6, $J_{4a,8a}$ = 12.4 Hz), 2.03, 1.97 (2s, 6H, 2 Ac), 0.91 (s, 9H, ^{t}Bu), 0.05 (s, 6H, $SiMe_2$).- **16**: δ = 6.18 (d, 1H, H-9 or H-10, $J_{9,10}$ = 10.1 Hz), 5.50 (ddd, 1H, H-9 or H-10, J = 2.1, 4.2, 10.1 Hz), 4.78, 4.62 (2d, 2H, CH_2OMe, J = 6.8 Hz), 4.24 (m, 2H, 2 H-13), 3.40 (s, 3H, OMe), 3.11 (ddd, 1H, H-7, $J_{7,8}$ = $J_{6,7}$ = 10.4, $J_{6',7}$ = 4.2 Hz), 2.40-1.12 (m, 11H), 1.38 (s, 3H, Me).- **2**: δ = 5.99 (d, 1 H, H-9 or H-10, $J_{9,10}$ = 10.3 Hz), 5.63 (ddd, 1H, H-9 or H-10, J = 2.0, 4.2, 10.3 Hz), 4.78, 4.63 (2d, 2H, CH_2OMe, J = 6.9 Hz), 3.82-3.64 (m, 2H, CH_2OH), 3.62 (s, 3H, COOMe), 3.40 (s, 3H, OMe) 3.15 (ddd, 1H, H-7, $J_{7,8}$ = $J_{6,7}$= 10.3, $J_{6',7}$ = 3.8 Hz), 2.17-0.83 (m, 12H), 1.28 (s, 3H, Me).
17. Separation by chromatography on silica gel (toluene/ethyl acetate, 97.5:2.5).
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