Natural Products

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Total Synthesis of Azithromycin**

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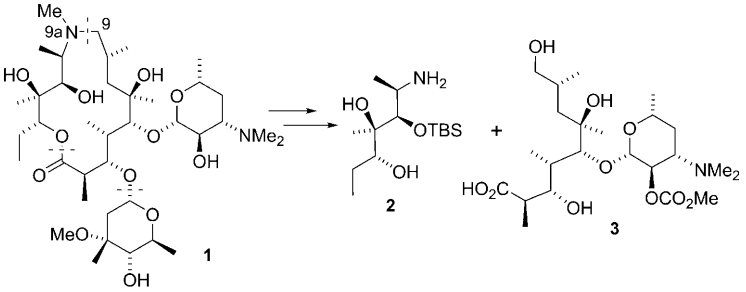
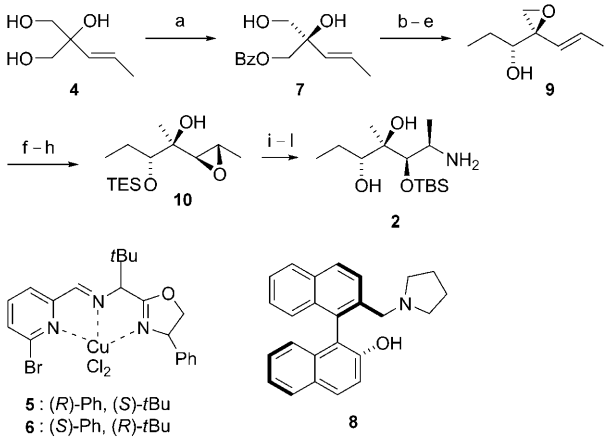
Azithromycin (**1**; see Scheme 1) is a semi-synthetic 15-membered macrolide antibiotic, which is derived from erythromycin A by a sequence of oxidation, Beckmann rearrangement, reduction, and N-methylation.[1] Azithromycin is the first azalide on the market and it displays the best antibacterial activity among its family members. In comparison with erythromycins, its beneficial properties stem from its improved acid stability, increased oral bioavailability, longer half-life, higher intracellular concentration, and broader antibacterial activity.[2] The X-ray crystal structure of a bacterial ribosome–macrolide complex suggests that azithromycin exerts antimicrobial activity by binding to the growing peptide in the trough of the 50S subunit to inhibit the protein biosynthesis.[3] As azithromycin possesses a stereochemically complex molecular architecture, similar to that of erythromycin A, and excellent physiological properties, it was seen as a great synthetic challenge by our research group. Moreover, we have recently established a highly enantioselective desymmetrization of 2-substituted glycerols,[4] which could be well suited to elaborate the stereogenic quaternary centers embedded in azithromycin. Herein, we report the first asymmetric total synthesis of azithromycin **1**.



Scheme 1. Retrosynthetic analysis of azithromycin (**1**). TBS = *tert*-butyldimethylsilyl.

A retrosynthetic disconnection of **1** at the lactone linkage and the C9–N9a bond would provide the western amine alcohol chain **2** and the eastern hydroxy carboxylic acid chain **3** (Scheme 1). Taking into consideration the previous syntheses of erythromycins[5] and the synthetic efficiency needed for azithromycin, the timing of the glycosylation steps appear to be critical to achieve more effective glycosylations and macrolactonization, and thus obviate extra protection/deprotection manipulation. Based on the retrosynthetic analysis, we propose to append desosamine during the eastern chain construction and cladinose after formation of the macrolide.

Our synthesis of azithromycin was initiated with the preparation of **2** through the desymmetrization method, asymmetric ethyl addition, and regioselective epoxide openings. According to the plan, the triol **4** was desymmetrized enantioselectively in the presence of the imine catalyst **5**[4a] to furnish the monobenzoate **7** with 91% *ee* in nearly quantitative yield (Scheme 2). After conversion of **7** into the corresponding epoxide through mesylation in a one-pot process, the generated epoxy benzoate was hydrolyzed, oxidized[6] and treated with Et_2Zn with the aid of the amino alcohol ligand **8**[7] to give an 11:1 separable mixture of the desired *R* alcohol **9**[8] and its diastereomeric *S* alcohol in 65% combined overall yield from **7**. The epoxy alcohol **9** was derivatized into the diasteromeric epoxide **10** in 71% yield along with 2–3% of its isomeric epoxide by reduction of the epoxy group with Red-Al, silylation of the secondary hydroxy group, and hydroxy-directing epoxidation. The epoxy group of **10** was amenable to regioselective substitution using NaN_3



Scheme 2. Preparation of the amine **2**. a) **5**, BzCl, Et_3N, THF, RT, 98% (91% *ee*); b) MsCl, Et_3N, CH_2Cl_2, −78°C; then DBU, RT; c) K_2CO_3, MeOH, RT, 69% (over 2 steps); d) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, 0°C; e) **8**, Et_2Zn, toluene, RT, 86% (over 2 steps); f) Red-Al, THF, 0°C; g) TESCl, imidazole, DMF, RT; h) mCPBA, CH_2Cl_2, −50°C, 71% (over 3 steps); i) NaN_3, $MgSO_4$, $MeOCH_2CH_2OH$, 110°C, 82%; j) TBSCl, imidazole, DMF, RT, 90%; k) Ph_3P, H_2O, THF, RT, 87%; l) HF/pyridine, THF, RT, 92%. Bz = benzoyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, mCPBA = 3-chloroperbenzoic acid, Ms = methanesulfonyl, Py = pyridine, Red-Al = bis(2-methoxyethoxy)aluminum hydride, TES = triethylsilyl.

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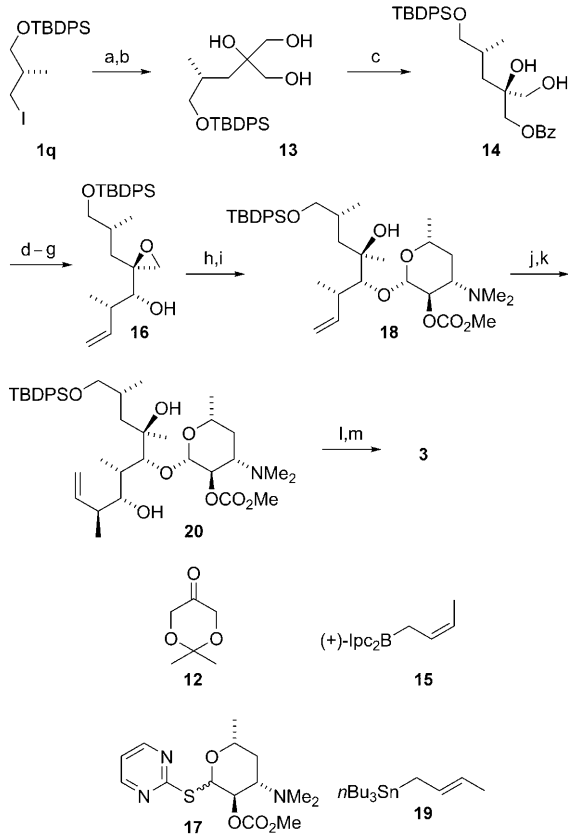
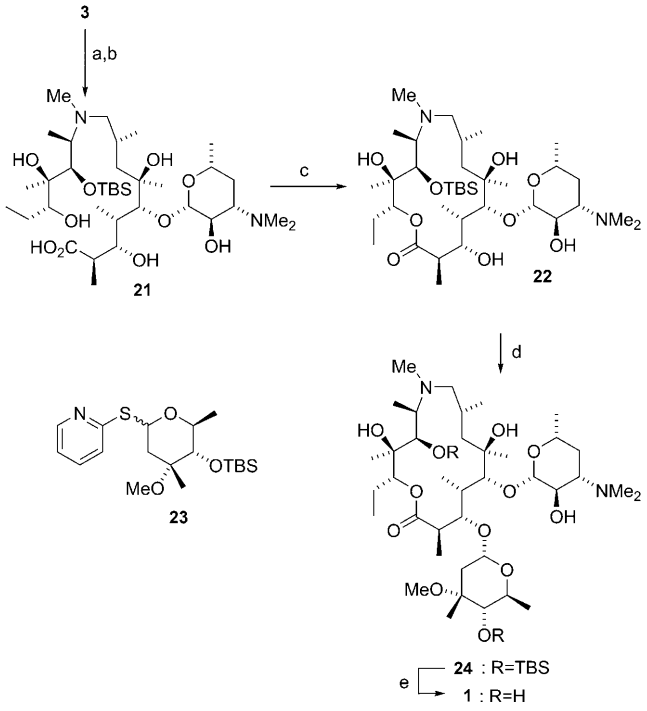
in the presence of $MgSO_4$ (probably acting as a coordinating cation supplier) in 2-methoxyethanol.[9] The prepared hydroxy azide was protected as a TBS ether, reduced to an amine, and desilylated to give the western amine segment **2** in 59% overall yield from **10**.

To construct the eastern carboxylic acid moiety **3**, we envisioned employing the desymmetrization protocol for the quaternary carbon center, crotylation reactions for the C2–C5 stereogenic centers, and the known chiral building block **11**[10] for the methyl substituent at C8. The desymmetrization substrate **13** was prepared from **11** in 62% yield by a sequence of transmetalation, addition of the generated alkyllithium to the ketone **12**, and hydrolysis[11] of the acetonide group (Scheme 3). Diastereoselective desymmetrization was carried out in the presence of the imine catalyst **6** and afforded the monobenzoate **14** in 94% yield along with 4% of its diastereomer (as expected).[4a] After conversion of **14** into the corresponding epoxy alcohol by the procedure applied to **7**, it was subsequently oxidized and then treated with crotylborane reagent **15**[12] and provided a 9:1 separable mixture of the epoxy alcohol **16** and its diastereomer in 79% combined yield. The epoxy group of **16** was reductively cleaved and the resultant diol was chemoselectively glycosylated at the secondary hydroxy group using 5 equivalents of pyrimidyl thiodesosaminide **17**[5a,b] in the presence of AgOTf[13] and delivered the desired stereoisomeric β-glycoside **18** in 60% yield along with 20% of recovered diol—no α-anomer or glycosylation at the tertiary hydroxy group was detected. For the requisite stereochemical installation of the substituents at C2 and C3, we resorted to the Felkin–Anh model utilizing the crotylation reagent **19**[14] as shown in the synthesis of erythromycin B that was developed by Martin and co-workers.[5c,d] Ozonolysis of **18** and subsequent crotylation gave alkene **20**, which had all the requisite functionalities installed, and 10% of other byproducts (presumably diastereomers of **20**). The olefinic double bond of **20** was cleaved by oxidation[15] and the resulting carboxylic acid was desilylated to form **3** in 77% overall yield.

With the synthesis of the two segments **2** and **3** completed, the endgame of our total synthesis would be carried out with their coupling, macrolactonization of the resulting carboxylic acid, and the second glycosylation of the macrolactone. Thereby, the primary hydroxy group of **3** was chemoselectively oxidized with Dess–Martin periodinane,[16] and the resultant aldehyde was coupled with **2** by reductive amination under hydrogenation conditions (Scheme 4). Next, formaldehyde was combined in the presence of an additional amount



Scheme 3. Preparation of the carboxylic acid **3**. a) sBuLi, THF, −98 °C; then **12**, −98 °C, 70%; b) $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$, CH_2Cl_2, 0 °C, 89%; c) **6**, BzCl, Et_3N, THF, RT, 94%; d) MsCl, Et_3N, −78 °C; then DBU, RT, 78%; e) K_2CO_3, MeOH, RT, 90%; f) $SO_3{\cdot}Py$, Et_3N, DMSO, CH_2Cl_2, 0 °C; g) **15**, THF, −78 °C, 71% (over 2 steps); h) Red-Al, THF, 0 °C, 87%; i) **17**, AgOTf, M.S. (4 Å), toluene, CH_2Cl_2, RT, 60% (20% recovered starting material); j) O_3, MeOH, −78 °C; then Me_2S, 0 °C; k) **19**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 77% (over 2 steps); l) OsO_4, Oxone, DMF, RT, 86%; m) TBAF, THF, RT, 90%. Ipc = isopinocampheyl, M.S. = molecular sieves, Oxone = potassium peroxymonosulfate, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, Tf = trifluoromethanesulfonyl.



Scheme 4. Completion of the total synthesis of azithromycin (**1**). a) Dess–Martin periodinane, CH_2Cl_2, 0 °C; b) **2**, H_2 (1 atm), 10% Pd/C (10 wt%), $NaHCO_3$, MeOH, RT; then 10% Pd/C (10 wt%), 37% formalin, RT, 70% (over 2 steps); c) 2,4,6-$Cl_3C_6H_2COCl$, DMAP, Et_3N, toluene, RT, 90%; d) **23**, $Cu(OTf)_2$, CuO, MeCN, RT, 53% (9% α-anomer and 24% recovered starting material); e) TBAF, THF, RT, 89%. DMAP = 4-dimethylaminopyridine.

of Pd/C. The one-pot coupling process was accompanied by removal of the carbonate group in the sugar ring and gave the monoglycosylated *seco*-acid **21** in 70% yield along with 3% of its diastereomer, which was formed from the enantiomer of **2**. Macrocyclization of **21** (at a concentration of 47 mM) under the reaction conditions developed by Yamguchi and co-workers[17] gave the 15-membered lactone **22** in 90% yield. The branched neutral sugar was attached to **22** using 8 equivalents of 2-thiopyridyl cladinoside **23**[5b,18] in the presence of $Cu(OTf)_2/CuO$[5c] and gave a 6:1 separable anomeric mixture of the TBS-protected azalides, in favor of the desired β-anomer **24**,in 53% yield along with 24% of the starting lactone **22**. After removal of the α-anomer by column chromatography, the purified β-anomer **24** was finally desilylated and gave azithromycin (**1**) in 89% yield.

A highly stereoselective total synthesis of azithromycin (**1**) has been accomplished from the readily available chiral building block **11** with a longest linear sequence of 18 steps. This work demonstrates that the enantioselective desymmetrization of 2-substituted glycerols is a powerful approach that can be used to achieve the challenging installation of hydroxy-substituted quaternary asymmetric centers.

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