Natural Product Synthesis

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Total Synthesis of the Antibiotic Branimycin**

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The nargenicin antibiotics[1] have repeatedly been the target of synthetic efforts over the past 20 years,[2–4] although only one synthesis has been completed so far.[2] Branimycin (**1**), which was isolated from the actinomycetes strain GW 60/1571 by the Laatsch research group,[5] is the most complex known member of this family. Biological tests have shown that branimycin is active against *Escherichia coli*, *Bacillus subtilis*, *Staphylococus aureus*, and in particular against *Streptomyces viridochromogenes*. The structure of **1**, which was elucidated by multidimensional NMR experiments only, is unusually complex, as 24 out of the 25 carbon atoms are either functionalized and/or stereogenic. In total, there are 12 stereocenters, 2 double bonds, 3 secondary OH groups, and 3 CH_2OMe functions. Additionally, the *cis*-fused dehydrodecalin core, the 7,12-ether bridge, and the nine-membered macrolide ring make **1** an attractive target for total synthesis.[6] Herein we report the first total synthesis of **1**, which also confirms the relative stereochemistry assigned by the Laatsch research group. Additionally, the absolute configuration of **1** has been established (Figure 1).

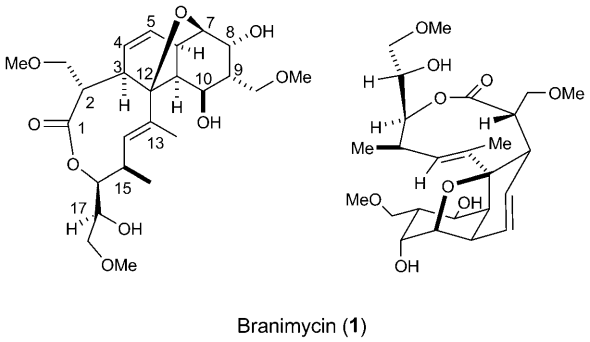
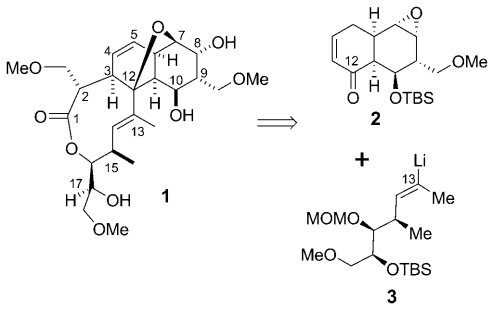
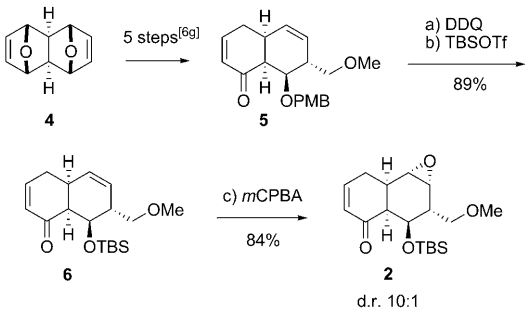


Figure 1. The structure of branimycin.

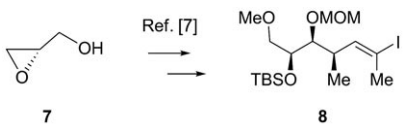
In keeping with the retrosynthetic plan outlined previously,[6c] we intended to assemble the target molecule by the addition of the organometallic side chain **3** to the *cis*-decalin ketone **2** (Scheme 1). We recently described[6g] the preparation of enantiopure decalin **5** by the desymmetrization of precursor **4** (Scheme 2). The protecting group was changed from PMB in **5** to TBS in **6** to ensure a high stereoselectivity in the ensuing epoxidation step (**6**→**2**). Side chain **8** was prepared in gram quantities from (*S*)-glycidol (**7**) by a modified version of our earlier approach[7] (Scheme 3; see the Supporting Information). Vinyl iodide **8** was metalated with *tert*-butyllithium to give **3**, and ketone **2** was then added to the organolithium species (Scheme 4). The primary adduct **9** could not be observed, as the ether bridge was directly closed to form **10**, presumably as a consequence of the lithium species acting as a Lewis acid catalyst. Protection of the OH group with a TBS group to give **11** was followed by allylic oxidation[8] to furnish enone **12**.



Scheme 1. Retrosynthetic analysis of **1**. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.



Scheme 2. Preparation of decalin ketone **2**. Reagents and conditions: a) DDQ, pH 7 buffer, CH_2Cl_2, 0–2 °C, 30 min, ultrasonic bath; b) TBSOTf, 2,6-di-*tert*-butylpyridine, THF, −78 °C, 1 h; c) *m*CPBA, CH_2Cl_2, 0 °C, 2 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *m*CPBA = 3-chloroperbenzoic acid, PMB = *para*-methoxybenzyl, Tf = trifluoromethanesulfonyl.



Scheme 3. Preparation of vinyl iodide **8**.

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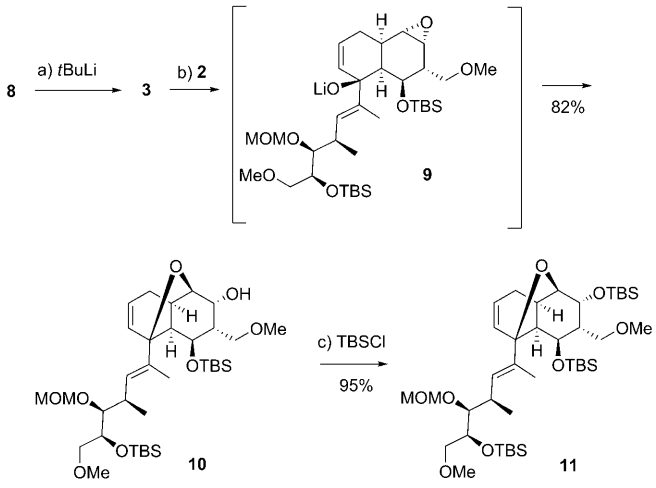
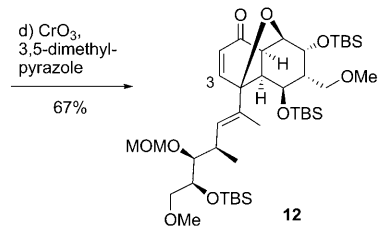




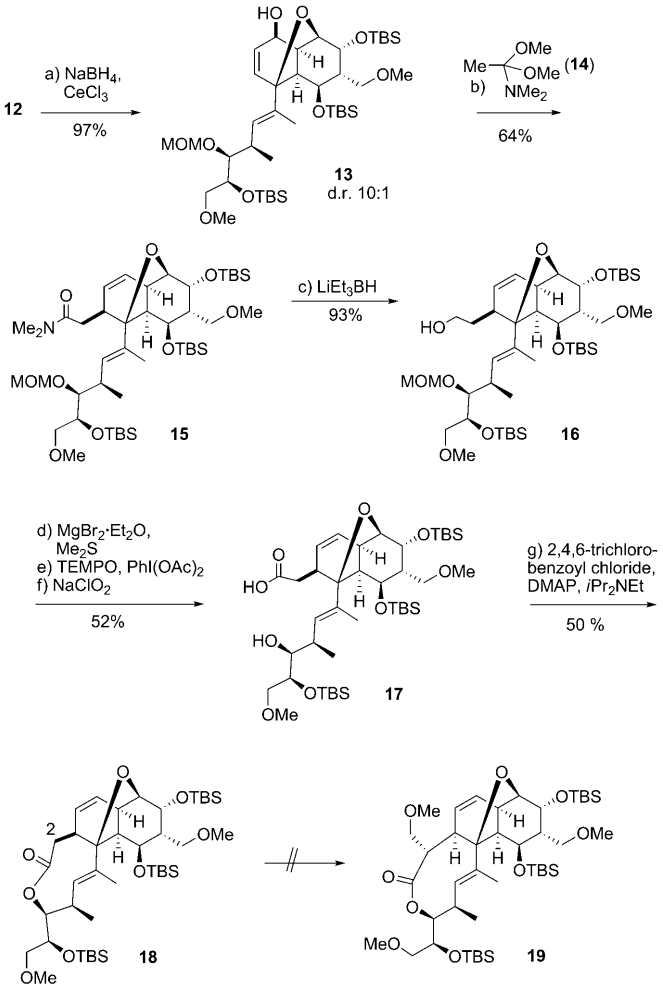
Scheme 4. Preparation of intermediate **12**. Reagents and conditions: a) **8** (1.7 equiv), *t*BuLi, THF, −78 °C, 2.5 h; b) **2** (1.0 equiv), THF, −78 °C, 5 min, warmed to 22 °C overnight; c) TBSCl, imidazole, DMF, 22 °C, 12 h; d) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −20 °C, 2 h, then **11** in CH_2Cl_2, −20 °C, 2 h. DMF = dimethylformamide.

The introduction of the side chain at C3 was first attempted by a Claisen–Eschenmoser rearrangement (Scheme 5).[9] Thus, enone **12** was reduced to the allylic alcohol **13** with high stereocontrol and then treated with acetamide acetal **14** in DMF under microwave irradiation to give amide **15**. The harsh conditions required prevented direct hydrolysis to the acid. Therefore, alcohol **16** was prepared by reduction with superhydride (lithium triethylborohydride). Removal of the MOM protecting group was followed by a selective oxidation of the primary hydroxy group with TEMPO[10a] to give the aldehyde and then, according to the procedure of Pinnick and co-workers,[10b] to *seco* acid **17**. Macrolactonization under modified Yamaguchi conditions[11] produced the nine-membered lactone **18**. Unfortunately all attempts to introduce the 2-CH_2OMe group were unsuccessful.

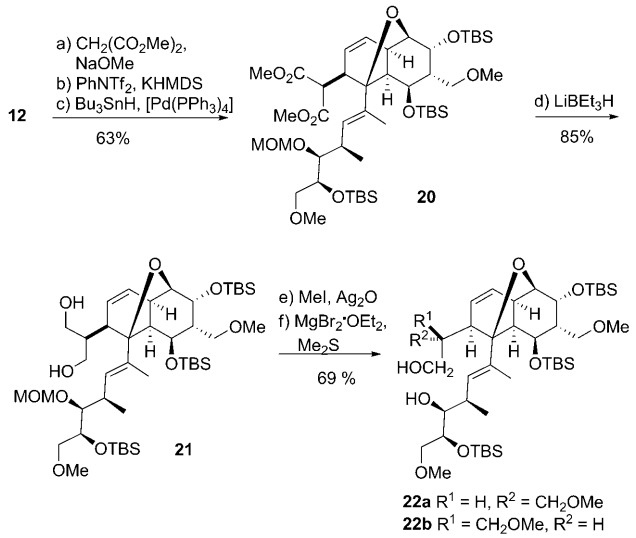
Therefore it was decided to install the crucial side chain by Michael addition (Scheme 6). In fact, the malonate anion added stereoselectively to the top face of enone **12**. The enolate was trapped by formation of a vinyl triflate. Reduction with Bu_3SnH under palladium catalysis gave diester **20** in good yield. Subsequent reduction furnished diol **21**, which was converted into a mixture of monomethyl ethers **22a/b**. The ratio of **22a/b** strongly depended on the conditions: Thus, MeI and Ag_2O[12] furnished a 1:1 mixture, whereas MeI/KHMDS gave a ratio of 1:4.

Selective cleavage of the MOM group with $MgBr_2$ enabled the two epimers to be separated by chromatography. In parallel experiments, the diastereomers **22a**,**b** were oxidized to *seco* acids **23a**,**b** in excellent yield (Scheme 7). Yamaguchi lactonization led to elimination of the 2-CH_2OMe group, presumably induced by the base present in the reaction mixture. Therefore, we switched to the virtually neutral Corey–Nicolaou–Gerlach[13] conditions, which did afford the nine-membered macrolactones **19** and **24** in acceptable yields. Treatment with TBAF in THF resulted in the least hindered 17-TBS group in **19**/**24** being removed first; the two remaining TBS groups were then subsequently removed to give branimycin (**1**) and its C2 epimer **25** in high yield.[14]

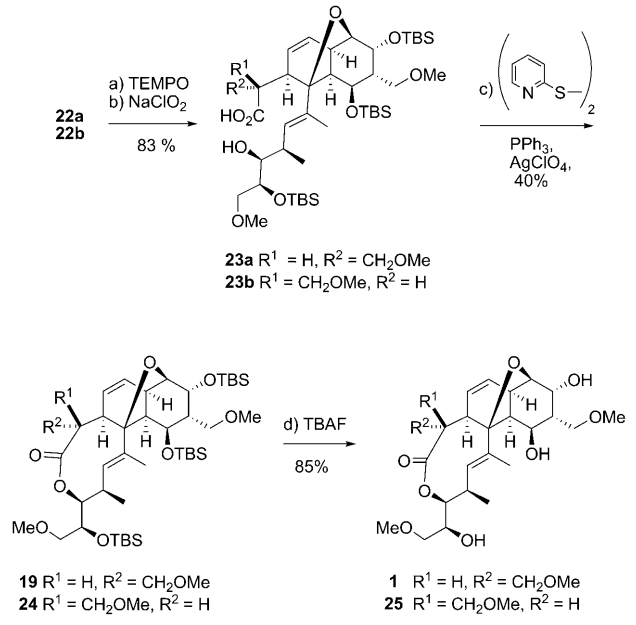
According to the usual criteria (^1H and ^{13}C NMR as well as IR and MS spectra, R_f values in three different solvents) our synthetic sample of **1** was identical to the authentic



Scheme 5. Preparation of macrolactone **18**. Reagents and conditions: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 12 h; b) **14**, DMF, microwave, 220 °C, 2 min; c) $LiBEt_3H$ (10 equiv), THF, 0 °C, 5 h; d) $MgBr_2 \cdot Et_2O$, Me_2S, CH_2Cl_2, 40 °C, 12 h (70% brsm); e) TEMPO (0.3 equiv), $PhI(OAc)_2$ (3 equiv), CH_2Cl_2, 22 °C, 2 h (87%); f) 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, *t*BuOH, H_2O, 18 °C, 40 min, (85%); g) 2,4,6,-trichlorobenzoyl chloride, iPr_2NEt, DMAP, toluene, 80 °C, 4 h. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, DMAP = 4-(dimethylamino)pyridine.



Scheme 6. Preparation of monomethyl ethers **22a**/**b**. Reagents and conditions: a) $CH_2(CO_2Me)_2$, NaOMe, MeOH, −21 °C→22 °C, 14 h (88%); b) $PhNTf_2$, KHMDS, THF, −78 °C→22 °C, 30 min, (93%); c) Bu_3SnH, $[Pd(PPh_3)_4]$, LiCl, 2,6-lutidine, THF, 22 °C, 14 h (78%); d) $LiBEt_3H$, THF, 0 °C→22 °C, 18 h; e) Ag_2O, MeI, 42 °C, 24 h, (99% brsm); f) $MgBr_2{\cdot}Et_2O$, Me_2S, CH_2Cl_2, 40 °C, 6 h, (70% brsm). HMDS = hexamethyldisilazane, brsm = based on recovered starting material.



Scheme 7. Completion of the synthesis. Reagents and conditions: a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 22 °C, 2 h (92%); b) 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*BuOH, H_2O, 15 °C, 30 min, (90%); c) $(PyS)_2$, PPh_3, $AgClO_4$, toluene, 85 °C, 2 h; d) TBAF, THF, 22 °C, 14 h. $(PyS)_2$ = 2,2′-dithiodipyridine, TBAF = tetra-*n*-butylammonium fluoride.

material. The optical rotation of the synthetic product ($[\alpha]_D^{25} = +88\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.04\ g\,cm^{-3}$, $CHCl_3$)) matched that of the natural product ($[\alpha]_D^{25} = +80\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.045\ g\,cm^{-3}$, $CHCl_3$)) and confirmed the absolute configuration depicted.

In conclusion we have developed the first synthesis of branimycin. The synthetic pathway is a convergent route with 22 steps in its longest linear sequence. The overall yield of the sequence is 2%. Our route is flexible with respect to the substituents and configurations of the individual stereogenic centers. More specifically, some of the hydroxy groups might be inverted, removed, or replaced by other functional groups, for example, amines. This should enhance the diversity of an envisaged library for detailed studies on the structure–activity relationship.

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[14] The relative configurations at the C2-position in **19**, **24**, **25**, and **1** were assigned by NOE experiments.

