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A diastereocontrolled route to the tetrahydropyran nucleus of pseudomonic acids

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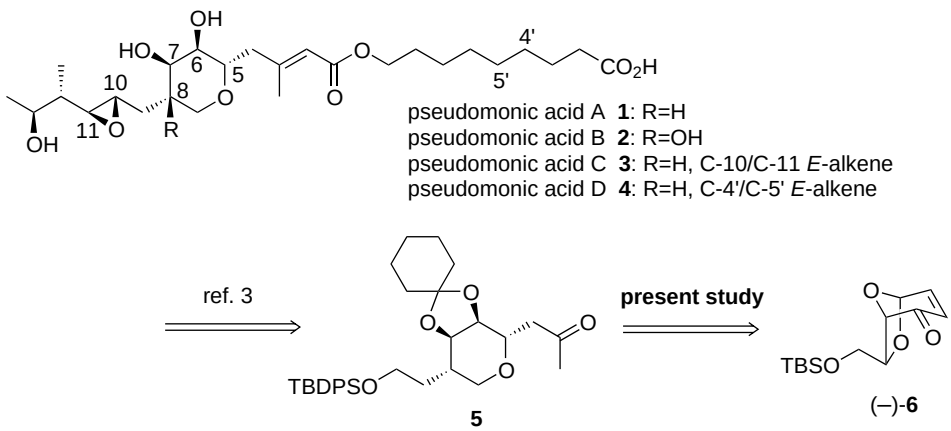
Abstract—A diastereocontrolled synthesis of the tetrahydropyran nucleus of pseudomonic acids has been achieved starting from a chiral building block, which we have developed. The key step is a convex-face reduction of the block having a biased framework which allowed assemblage of the most important core in a completely diastereoselective manner.

The pseudomonic acids **1**–**4** are a family of C-glycopyranoside antibiotics produced by *Pseudomonas fluorescens* and are potent inhibitors of gram-positive aerobic bacteria.[1,2] All four pseudomonic acids are structurally related and three of them contained a common tetrahydropyran ring flanked by α-*cis* side chains at C-5 and C-8 as well as β-*cis* side chains at C-6 and C-7. Due to their unusual structure and potent biological activity, a number of racemic and non-racemic syntheses have been reported to date.[1] However, few have accomplished the construction of the most important common tetrahydropyran nucleus responsible for inhibitory activity of the three pseudomonic acids in complete diastereoselection with the proper absolute configuration. Here, we report a diastereocontrolled route to the most important tetrahydropyran nucleus[3] **5**, which was previously obtained from D-arabinose and used as the key intermediate of pseudomonic acids A **1** C **3** by Fleet and coworkers,[3] in enantiopure forms starting from the chiral building block **6**. Although the basic concept employed in the present synthesis is rather common, complete diastereocontrol could be attained on the basis of inherent diastereoselective nature of the chiral building block which we have developed for the sugar synthesis[4,5] by employing either catalytic asymmetric synthesis[6] or enzymatic resolution[7] (Scheme 1).

Thus, the reaction of enantiopure enone (–)-**6** with sodium borohydride in the presence of cerium (III) chloride[8] afforded single *endo*-allyl alcohol **7**, $[\alpha]_D^{28}$ +2.9 (*c* 1.0, $CHCl_3$), diastereoselectively by reduction from



Scheme 1.

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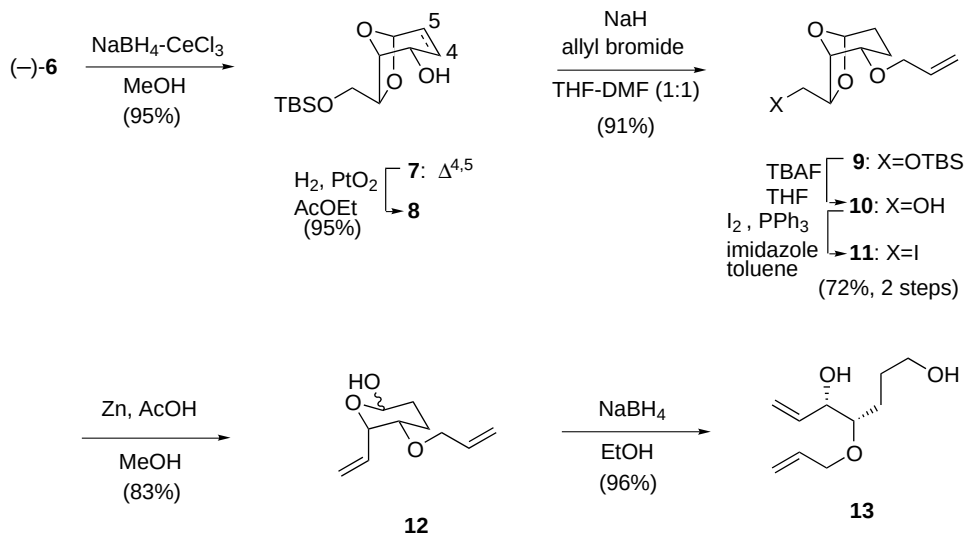
the convex-face of the molecule. After hydrogenation of **7**, the resulting **8**, $[\alpha]_D^{29}$ +16.5 (*c* 1.0, $CHCl_3$), was transformed into allyl ether **9**, $[\alpha]_D^{26}$ +1.8 (*c* 1.6, $CHCl_3$), which was further transformed into iodide **11**, $[\alpha]_D^{27}$ −18.6 (*c* 1.2, $CHCl_3$), via primary alcohol **10**, $[\alpha]_D^{29}$ +45.0 (*c* 1.5, $CHCl_3$), by sequential desilylation and iodination.[9] Upon exposure to zinc in methanol containing acetic acid[4,5] at room temperature, **11** furnished hemiacetal **12**, by reductive cleavage of the iodo–ether linkage, which was further reduced with sodium borohydride to afford the diol **13**, $[\alpha]_D^{28}$ −4.8 (*c* 1.0, $CHCl_3$), having a 1,7-diene system. Overall yield of **13** from the chiral building block (−)-**6** was 47% in seven steps. The most important stage for the construction of the target molecule has been virtually done at this stage (Scheme 2).

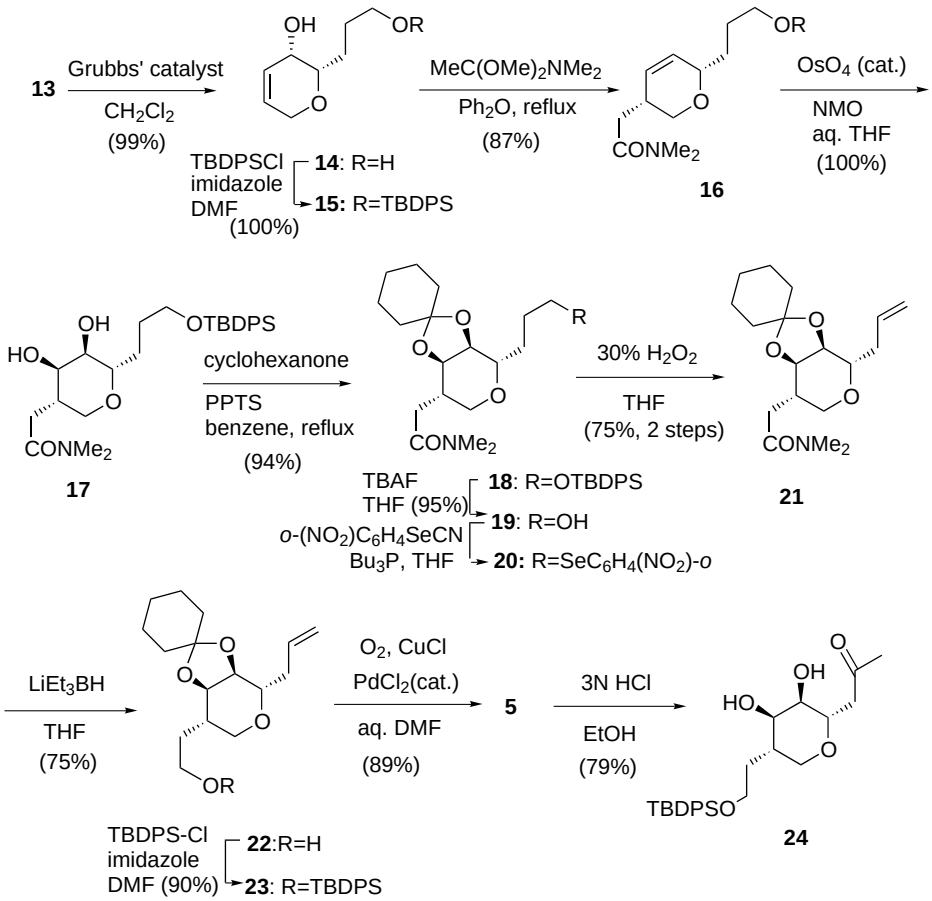
Conversion of the diene **13** into the pyran ring was carried out in a straightforward manner employing standard ring-closing metathesis reaction.[10,11] The reaction took place very easily when 0.02 M solution of **13** in dichloromethane was refluxed in the presence of 10 mol% of Grubbs' catalyst[12] to furnish the diol **14** in nearly quantitative yield. After selective protection of the primary hydroxy functionality of **14** as a silyl ether, the resulting **15**, $[\alpha]_D^{26}$ +85.0 (*c* 1.1, $CHCl_3$), was heated with dimethylacetamide dimethylacetal in diphenyl ether at 280°C to initiate the Eschenmoser–Claisen rearrangement[13] to give rise to the *cis*-2,5-disubstituted dihydropyran **16**, $[\alpha]_D^{24}$ −19.2 (*c* 1.2, $CHCl_3$). Among the solvents tested, the rearrangement reaction proceeded best in refluxing diphenyl ether. As expected, dihydroxylation of **16** under standard conditions[1] proceeded diastereoselectively from the opposite face of the 2,5-substituents to furnish the single diol **17**, $[\alpha]_D^{23}$ +1.3 (*c*1.7, $CHCl_3$), which was transformed into primary alcohol **19**, via **18**, $[\alpha]_D^{23}$ −4.1 (*c* 1.3, $CHCl_3$), by seqential ketalization and desilylation. Overall yield of **19**, $[\alpha]_D^{21}$ −4.4 (*c* 1.2, $CHCl_3$), from diene **13** was 76% in six steps.

Having installed the four functionalities in a completely diastereoselective manner on the tetrahydropyran ring in the proper configuration, we next carried out the conversion of **19** into the known intermediate[3] **5**, which has been used for the synthesis of pseudomonic acids A **1** and C **3**, to confirm the structure of the synthetic product. Thus, primary alcohol **19**, was first dehydrated by employing Grieco conditions[14] to give terminal olefin **21**, $[\alpha]_D^{28}$ −2.8 (*c* 0.5, $CHCl_3$), which was then reduced with lithium triethylborohydride to convert the amide functionality into the primary hydroxy functionality[15] in one step to give **22**, $[\alpha]_D^{21}$ −16.0 (*c* 1.4, $CHCl_3$). After silylation, resulting silyl ether **23**, $[\alpha]_D^{25}$ −3.3 (*c* 2.3, $CHCl_3$), was subjected to the Wacker oxidation under the Tsuji conditions[16,17] to give the target ketone **5** without difficulty. Thus, on stirring with copper(I) chloride (1 equiv.) in aqueous DMF (60%) in the presence of a catalytic amount of palladium(II) chloride (10 mol%) under oxygen at room temperature, **23** furnished **5**, $[\alpha]_D^{27}$ −1.0 (*c* 1.5, $CHCl_3$), in 89% yield. Since its specific rotation value was not reported, the product **5** obtained was hydrolyzed with ethanolic hydrochloric acid[18] so as to obtain the known diol **24**, $[\alpha]_D^{26}$ +19.1 (*c* 0.7, $CHCl_3$) {lit.:[3] $[\alpha]_D^{20}$ +18.6 (*c* 2.0, $CHCl_3$)}. The key pyran nucleus **5** of pseudomonic acids was thus obtained from the chiral building block (−)-**6** with complete diastereoselection in 16% yield in 18 steps (Scheme 3).

In summary, we report a diastereocontrolled route to the tetrahydropyran nucleus of pseudomonic acids in enantiopure forms utilizing a chiral building block originally developed for the construction of sugar molecules. Although the present synthesis connects to the known intermediate to complete a formal synthesis of pseudomonic acids A and C, the methodology employed may be shortened and improved in more ways for the synthesis of the pseudomonic acids as well as medicinally interesting unnatural pseudomonic acid derivatives[19] in diastereselectively in enantiopure forms.



Scheme 2.



Scheme 3.

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