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SYNTHETIC APPLICATION OF A SUBSTITUENT CONTROLLED CLAISEN REARRANGEMENT. PREPARATION OF ADVANCED CHIRAL INTERMEDIATES FOR THE SYNTHESIS OF PSEUDOMONIC ACIDS

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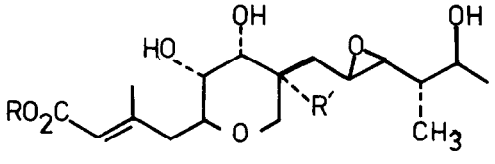
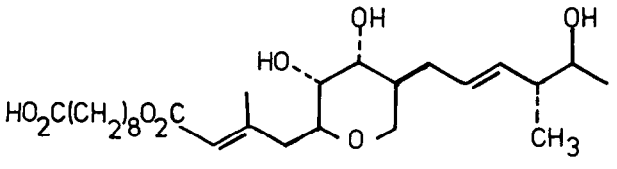
Abstract: A substituent controlled Claisen rearrangement is employed as the key reaction for a facile construction of chiral intermediates for the synthesis of pseudomonic acids from diacetyl-L-arabinal.

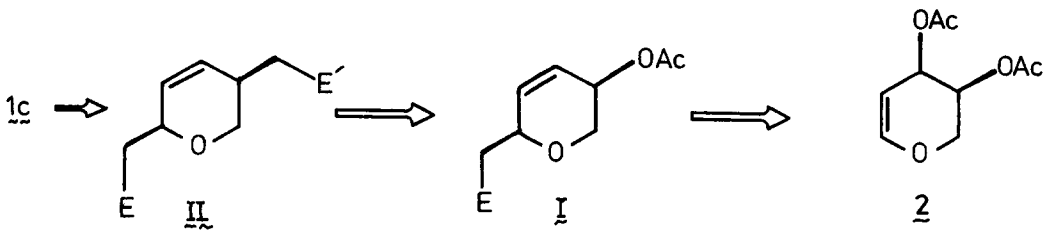
Pseudomonic acids A(1a), B(1b), C(1c) and D(1d) are produced by a strain of Pseudomonas flourescens.[2] In addition to functioning as a competitive inhibitor of isoleucyl-tRNA synthetase, the major metabolite, 1a, is an effective antimicrobial agent.[3] The novel C-glycopyranoside ring system and diverse functionality have prompted synthetic activity. Pioneering studies by Kozikowski et al. have resulted in the first total synthesis of racemic pseudomonic acid C.[4] More recent endeavors in several laboratories have focused on chiral synthesis from carbohydrates.[5,6] In such an approach,[7] it is important to avoid the extensive manipulations of the carbohydrate nucleus which are often required to selectively introduce the desired functionalities. This pyranocide strategy can unduly protract an otherwise elegant synthesis. We have recently communicated an approach which avoids these aforementioned problems.[8] The strategy for 1a and 1c, outlined in equation 1, calls for the sequential transformation of the two C-OAc bonds of diacetyl-L-arabinal (2) to the two C-C bonds of II. While both steps require retention of absolute stereochemistry, the first transformation requires transposition of allylic stereochemistry while the second demands retention.





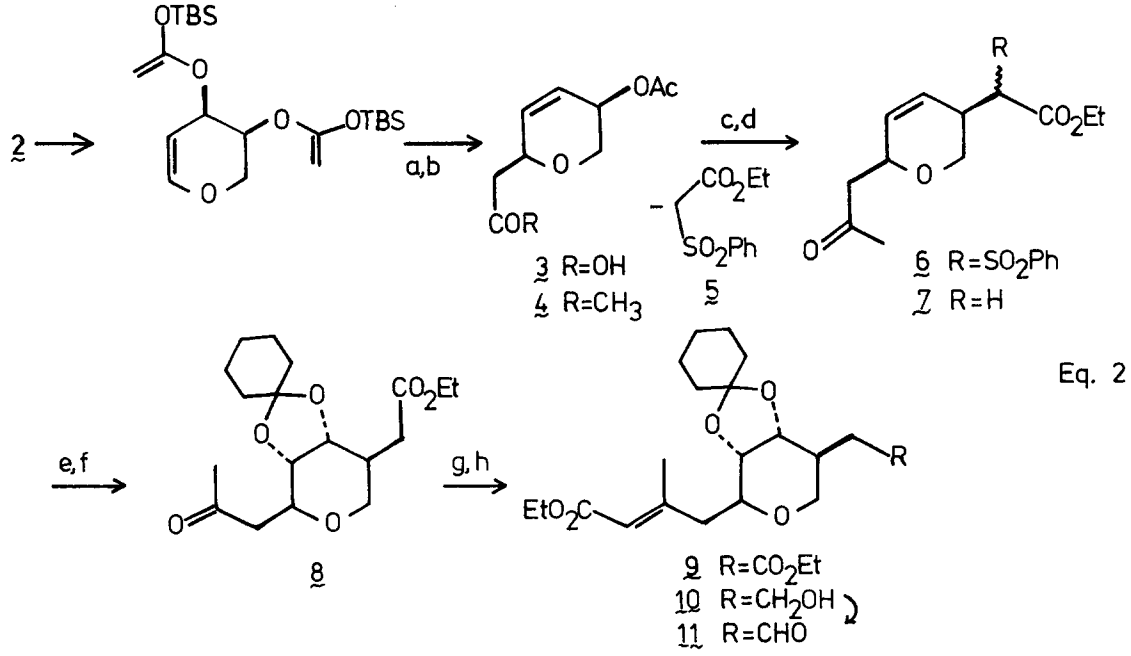
1A R=$(CH_2)_8COOH$; R'=H
1B R=$(CH_2)_8COOH$; R'=OH
1D R=$(CH_2)_4CH{=}CH(CH_2)_2COOH$; R'=H

1c



Eq. 1

Diacetyl-L-arabinal is readily available in two conventional steps from inexpensive L-arabinose.[9] The first key step involves our recently discovered substituent controlled "mono-Claisen" rearrangement[8] (Eq. 2) of 2. Generation of the bis-ketenesilyl acetal of 2 and rearrangement according to the general Ireland ester enolate Claisen procedure[10] produced unstable acid 3 after desilylation of the intermediate mono-ketenesilylacetal-mono-silyl ester. Here the two similar acetates are chemically differentiated without resort to protection by virtue of the accelerated rate of the first Claisen rearrangement. We have recently attributed this rate enhancement to the "vinylogously anomeric" nature of the cleaving C-O bond[11] with respect to the ring oxygen substitutent.

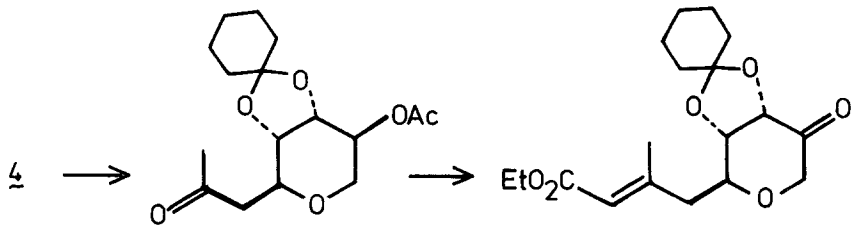


Eq. 2

Reaction Conditions: a) 60°C, 6hr; KF, 64%; b) $SOCl_2$; o-MeC_6H_4COOH, Et_3N; CH_3MgBr/THF, -78°C, 42%; c) $Pd(dppe)_2$, 5, THF, 85%; d) 6% Na(Hg), MeOH, NaH_2PO_4, 81%; OsO_4, NMO, 73%; f) cyclohexanone, pTSA, benzene, 83% g) NaH, $(EtO)_2P(O)CH_2COOEt$, 81%; 3/1, E/Z; h) n-BuAl(H)i-Bu_2, THF, -78°, 86%.

After conversion of acid 3 to the methyl ketone 4, the second key transformation was accomplished by π-allylpalladium mediated displacement[12,13] of the allylic acetate with sulfonyl ester anion 5 to give 6 (1/1 mixture of diastereomers at the sulfone center). After reductive desulfonylation,[14] a single isomer 7 was isolated. This observed retention of both absolute and allylic stereochemistry can be attributed to backside attack of the nucleophile at the center remote from the side chain in the intermediate α-π-allylpalladium complex.[12] Catalytic osmylation[15] of 7, followed by protection of the resultant diol as the cyclohexylidene derivative, gave 8 in good yield. Standard olefination gave 9 along with the corresponding Z isomer in a 3/1 ratio. Interestingly, the two esters of 9 were readily differentiated. Reduction of 9 with the "ate"-complex derived from n-BuLi and DIBAL[16] gave a 1/1 mixture of alcohol 10 and aldehyde 11 along with a small amount of recovered 9. No products of reduction of the unsaturated ester were detected. Known aldehyde 11 has been converted in both racemic[4a] and chiral[5b] forms to 1a to 1c by a sequence of olefination, ester exchange, and deprotection. Thus, the advanced intermediate 11 is available in chiral form in nine steps from diacetyl-L-arabinal. Note that although none of the original C-OH bonds from arabinose remain, no conventional protection-deprotection steps were employed to manipulate these C-O bonds.

Intermediate 4 is ideal for the approach to the hydroxyl bearing pseudomonic acid B (1b) (Eq. 3). Osmylation and protection as above gave 12. After olefination, the acetate was saponified [NaOEt, EtOH, 0°C] and the resultant alcohol oxidized (SO_3·pyr/DMSO)[17] to give ketone 13[6a] in good overall yield.



12 13 Eq. 3

This unified approach to the pseudomonic acids is short and efficient and demonstrates the utility of the substituent controlled Claisen rearrangement for rapid and selective manipulation of carbohydrate precursers.[18]

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