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AN APPROACH TO THE ENANTIOCONTROLLED SYNTHESIS OF PSEUDOMONIC ACIDS VIA A NOVEL MONO-CLAISEN REARRANGEMENT

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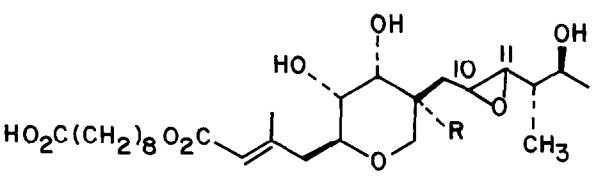
Abstract: A short, efficient approach to a key chiral intermediate for the synthesis of pseudomonic acids A and C is delineated.

Pseudomonic acids A(1a), B(1b), and C(2) are members of a novel class of "C-glycopyranoside" antimicrobial agents which have recently attracted synthetic attention.[2] Presently, we wish to report a short efficient strategy towards the total synthesis of optically active pseudomonic acids. The sequence is highlighted by a novel controlled mono-Claisen rearrangement and a highly regioselective π-allylpalladium mediated displacement.

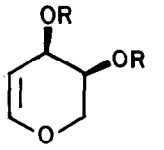
Diacetyl-(L)-arabinal (3)[3] was converted to the bis-ketenesilylacetal 4 and warmed to 60°C according to the Ireland ester-enolate Claisen rearrangement method.[4] Over a period of ~5h, smooth conversion to a major rearranged product 5 was observed by 300 MHz NMR. The identity of 5 was confirmed by direct desilylation and methylation (KF, $KHCO_3$, H_2O, HMPA, CH_3I). After flash chromatography, compound 7 was isolated in 55% overall yield from 3. Careful inspection of the crude methylation product revealed the presence of ~5% doubly rearranged product 6.

The rearrangement of 4 to 5 is a unique example of a selective mono-Claisen rearrangement in which the rate of a second similar Claisen rearrangement (5 → 6) is much slower under the reaction conditions. Although the reasons for this interesting selectivity are unclear at this time,[5] in practice, the mono-Claisen rearrangement obviates the need for selective differentiation of the two hydroxyl groups, a difficult task at best, in this case.

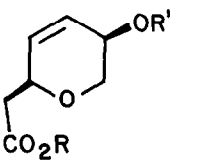
Palladium mediated allylic acetate displacement provided an ideal method for introduction of a second chemodifferentiated side chain with allylic retention and retention of stereochemistry. Alkylation of 7 with sodiodiethylmalonate using 5 mole % $Pd(0)dppe_2$[6] was unusually facile (<45 min, 25°C, THF). After semi-preparative HPLC, essentially a single regio- and stereoisomer was isolated in 96% yield.[7] Structure 8 was confirmed by extensive ^{1}H-NMR decoupling, as well as an off-resonance ^{13}C-NMR experiment. In particular, H_1 (δ 4.53) was coupled vicinally to H_6 and H_6' (5 Hz, 8 Hz) and H_2 (1.5 Hz), and allylically to H_3 (2 Hz). In contrast, H_4 (δ 2.78) was coupled to H_7 (10 Hz), H_{5e} and H_{5a} (1.8 Hz, 4 Hz), H_3 (5 Hz), and H_2 (<1 Hz). In addition, H_1 and H_4 exhibited a small long range coupling constant (J = <1 Hz). These coupling constants rule out



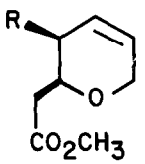
1a R = H
1b R = OH
2 R = H, Δ10,11



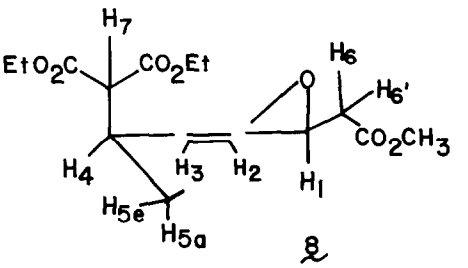
3 R = Ac
4 R = [Si(CH3)2OC(=CH2)]



5 R = Si(CH3)3, R' = [Si(CH3)2OC(=CH2)]
7 R = CH3, R' = Ac



6 R = CH2CO2CH3
9 R = CH(CO2Et)2



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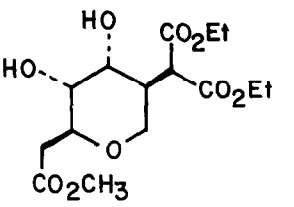

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regioisomer 9 and are fully consistent with the indicated conformation, which minimizes 1,3-diaxial-like interactions.

Finally, catalytic osmylation of 8[8] gave a single cis-diol 10 in nearly quantitative yield. Appending of suitably functionalized side chains to provide an enantiocontrolled synthesis of pseudomonic acids A(1a) and C(2) is in progress.[9,10]

References

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2) For references regarding isolation, activity, and synthesis see: Snider, B. B.; Phillips, G.B. J. Amer. Chem. Soc. (1982), 104, 1113.
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5) For references and an evaluation substituent effects on the Claisen rearrangement see: Carpenter, B. K.; Burrows, C. J. J. Amer. Chem. Soc. (1981), 103, 6983.
6) Pd(0)dppe2 = Palladium(0)bis-1,2-diphenylphosphinoethane. See: Trost, B. M. Acct. Chem. Res. (1980), 13, 385.
7) A small amount of another product (<1%) of undetermined structure was detected. For a study on substitution of carbohydrate derived allylic acetates see: Baer, H. H.; Hanna, Z. R. Cand. J. Chem. (1981), 59, 889.
8) Van Rheenan, V.; Kelly, R. C.; Cha, O. Y. Tetrahedron Lett. (1976), 1973.
9) Satisfactory elemental analysis and/or high resolution MS obtained for all new compounds.

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