Free-Radical Addition–Fragmentation Reactions in Synthesis: A "Second Generation" Synthesis of (+)-Pseudomonic Acid C

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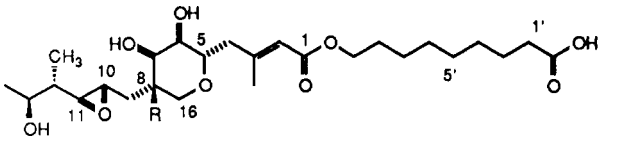
Summary: A highly convergent approach to (+)-pseudomonic acid C, which utilizes a free-radical addition–fragmentation process as the key step, has been demonstrated.

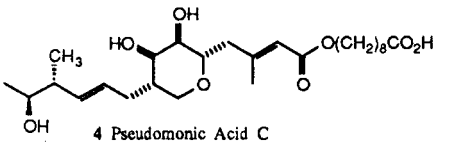
Sir: The pseudomonic acid family of antibiotics,[1] such as pseudomonic acids A, B, C, and D, have attracted intense synthetic interest[2] due to their unusual structures and mode of action.[3] Of these substances, pseudomonic acid C (4) is perhaps the most promising for further development, as the pseudomonic acids possessing a C_{10}–C_{11} epoxide function are rapidly deactivated in vivo.[4] We have previously reported a total synthesis of pseudomonic acid C[2h] in which stereoselective free-radical allylation[5] played a key role. We now describe a much more convergent approach to this material in which the entire C_9–C_{14} appendage is added to the pyranose core of pseudomonic acid C in a single step and with an extremely high level of stereoselectivity. The approach is outlined antithetically in eq 1 below. Thus is was envisioned, based upon previous work from our laboratory,[6] that a suitably functionalized allyl fragment **5**, with X = SPh, SOPh, or SO_2Ph, could be coupled via an addition–fragmentation mechanism with a carbon-centered radical derived from iodide **6**; a process which would not be expected to be efficient using a stannane of general structure **5**.[7]



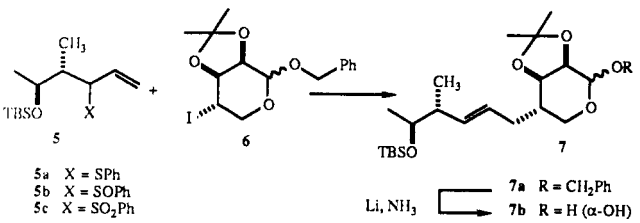
1 R = H Pseudomonic Acid A

2 R = OH Pseudomonic Acid B

3 R = H, $C_{4'}$-$C_{5'}$ Alkene Pseudomonic Acid D



4 Pseudomonic Acid C



5a X = SPh
5b X = SOPh
5c X = SO_2Ph

Li, NH_3

7a R = CH_2Ph
7b R = H (α-OH)

Preparation of the iodide **6** (note Scheme I) began with the known[2h] 1-*O*-benzyl-2,3-isopropylidene-L-lyxopyranose **8a**. Since previous work from our laboratories had demonstrated that the sole free hydroxyl in **8a** could not be converted to halogen or selenylphenyl,[2h] an indirect approach was necessary.[8] Exposure of **8a** to methanesulfonyl chloride in pyridine at 23 °C gave the corresponding mesylate **8b**, which was treated with 1:1 1 N HCl/THF to give diol **9** in 87% overall yield from **8a**. Epoxide formation to yield **10** was accomplished in 96% yield by treatment of **9** with potassium *tert*-butoxide in THF at room temperature for 30 min. Reaction of **10** with 2.0 N HI in acetone at reflux, followed by conversion of the resulting vicinal diol to the corresponding acetonide derivative (dimethoxypropane, pTsOH, acetone), furnished the desired iodide **6** in 85% overall yield from **10**.[9]

The synthesis of sulfone **5c** is outlined in Scheme II. The route began with the known,[2h] readily available ester **11** (utilized in our previous route), which was homologated to allylic alcohol **12** in a one-pot operation (65% yield) via reduction and in situ Emmons reaction according to the Takacs protocol,[10] followed by the addition of 2.1 equiv of $(iBu)_2AlH$ and workup (methanol, then saturated aqueous Rochelle salt). Conversion of **12** to sulfone **5c** was initiated by [2,3] sigmatropic rearrangement of the derived sulfenate (1.0 equiv of *n*-BuLi, THF, 0 °C; PhSCl) via the

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(3) (a) O'Halon, P. J.; Roberts, N. H.; Tyler, J. W. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2655. (b) Bactoroban, Proceedings of an International Symposium; Dobson, R. L.; Leyden, J. J.; Noble, W. C.; Price, J. E., Eds.; excerpta Medica: Amsterdam, The Netherlands, 1985; pp 7–8. (c) Crimmin, M. J.; O'Halon, P. J.; Rogers, N. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 549.

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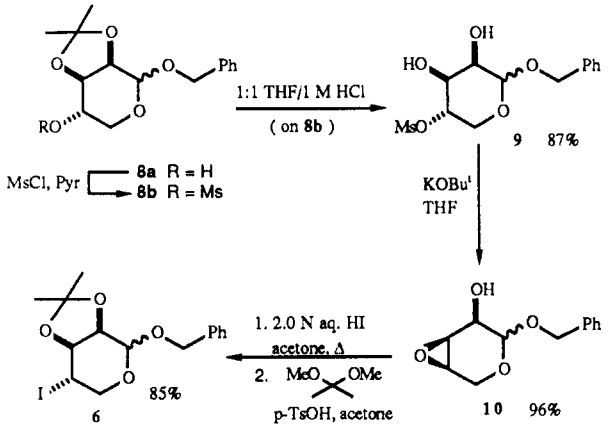
(8) Our previous experiences[2h] regarding the difficulty of such displacement reactions were reconfirmed in the course of this work. Also in accord with previous experience,[6] thionocarbonates derived from **8a** were found to be unsatisfactory in the free-radical reactions described herein.

(9) The corresponding bromide can also be prepared in high yield using a parallel process; however, initial results on coupling reactions using this substrate were not encouraging.

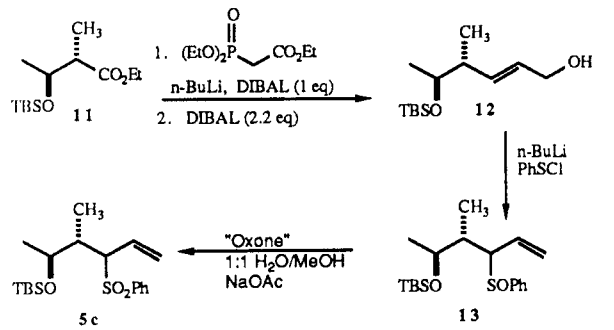
(10) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257.

0022-3263/89/1954-5845$01.50/0

Scheme I



Scheme II



general procedure of Evans,[11] followed by oxidation with Oxone[12] to give the desired sulfone as a ca. 2:1 mixture of epimers.[13]

The desired one-electron union of **5c** and **6** proved much more difficult than anticipated and required scrupulous attention to experimental detail for success. For example, exhaustive investigation using chemical initiation with initiators such as AIBN or ACN[14] at 80–110 °C in the presence of 1.0 equiv of hexabutylditin[6] failed to afford detectable amounts of the desired coupling products. Failure was also encountered using the Hart protocol[15] with initiation from stoichiometric amounts of bis(trimethylstannyl) benzopinacolate.

Better results were obtained using photochemical initiation. For example, when a mixture of 3 equiv of sulfone **5c**, 1 equiv of iodide **6**, and 1.5 equiv of hexabutylditin in toluene was irradiated (450-W Hanovia lamp with Pyrex filter) for 12 h, 20% of the desired addition product was isolated, along with 60% of the product of simple reduction of iodide **6** and allylically transposed sulfone. Finally it was found that slow addition (syringe pump) of a THF solution (0.54 M in **5c**) of 1.0 equiv of sulfone **5c** and 0.5 equiv of hexabutylditin to an irradiated solution of 1.0 equiv of iodide **6** and 0.5 equiv of hexabutylditin (0.54 M in THF) under argon afforded the desired coupling product **7a** in 74% isolated yield (note eq 1).

NMR analysis indicated a 13:1 mixture of trans/cis C_{10}–C_{11} geometric isomers. Reductive cleavage (Li, NH_3 (l), THF) of the benzyl group gave the α-lactol **7b**, which was spectroscopically indistinguishable (^{1}H NMR, ^{13}C NMR, HRMS) from material previously prepared in our laboratories and subsequently converted to (+)-pseudomonic acid C.[2h] HPLC analysis of the UV-active 1-*O*-benzoyl derivative again revealed a 13:1 mixture of trans/cis C_{10}–C_{11} geometric isomers. Isomeric substances resulting from incomplete facial selectivity in construction of the C_8 stereogenic center were not detected.

The successful realization of a "second generation" total synthesis of (+)-pseudomonic acid C according to the free-radical addition–fragmentation process described herein again demonstrates the power of such reactions in organic synthesis[16] and also suggests that such reactions will find continuing application.

Acknowledgment. Financial support of this research by the NSF (Grant CHE 8312729) is gratefully acknowledged.

Supplementary Material Available: Full experimental details and spectral and physical data for compounds described herein (24 pages). Ordering information is given on any current masthead page.

(11) Evans, D. A.; Andrews, G. L. *Acc. Chem. Res.* **1974**, 7147.
(12) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(13) The major sulfone (stereochemistry unassigned) could be isolated by column chromatography (3% THF/hexanes; silica gel) for purposes of characterization. For synthetic purposes, the 2:1 mixture was employed.
(14) (a) Overberger, C. G.; Biletch, J.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1943**, *75*, 2078. (b) For a discussion of "some properties of radical reactions important in synthesis", note: Walling, C. *Tetrahedron Symp.* **1985**, *41*, 3887.
(15) Hart, D. J.; Seely, L. S. *J. Am. Chem. Soc.* **1988**, *110*, 1631.
(16) For the use of a free radical addition-fragmentation process for the construction of $PGF_{2\alpha}$ see: Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

Palladium-Catalyzed Polyene Cyclizations of Trienyl Triflates

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Summary: Spirotricyclic dienones are conveniently prepared by palladium-catalyzed cyclizations of enol triflate derivatives of 2-dienyl-1,3-cyclohexanediones. The use of chiral (nonracemic) ligands allows assembly of these products with moderate enantioselectivity, demonstrating a potentially powerful new method for catalytic asymmetric construction of quaternary carbon stereocenters.

Sir: Our laboratory recently initiated a program aimed at developing a polyene cyclization chemistry mediated by transition metals.[1,2] A generalized spirocyclic example of

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