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Stereoselective Synthesis of Methyl Monate C

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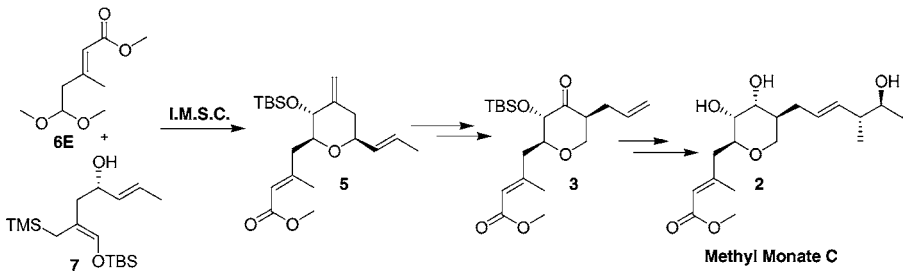
ABSTRACT



The stereoselective synthesis of methyl monate C 2 is described using as a key step an ene-intramolecular modified Sakurai cyclization (IMSC) reaction to prepare tetrahydropyran 5. An asymmetric allylic alkylation, followed by a cross-metathesis, enables the insertion of the right-hand side chain.

Pseudomonic acid C **1**, a potent antibiotic produced by a strain of *Pseudomonas fluorescens*, acts as a competitive inhibitor of isoleucyl-tRNA synthetase and is an effective antimicrobial agent against Gram-positive bacteria such as *Staphilococcus aureus*, *Neisseria gonorrhea*, and mycoplasmal pathogens[1] (Figure 1).

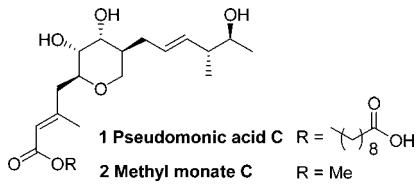


Figure 1. Pseudomonic acid and methyl monate C.

The absolute and relative stereochemistries have been determined by spectroscopic studies[2] and by X-ray diffraction analysis.[3] Besides its striking pharmacological properties, pseudomonic acid C also presents a challenging structure, embodying a tetrasubstituted pyran nucleus with four contiguous stereogenic centers, two of them occupying an axial position. The enhanced biological activity of **1**, coupled with its intricate architectural framework, has spurred the interest of numerous research groups worldwide, resulting in several elegant total syntheses of this natural product and its congeners.[4]

Our interest in sugar-containing natural products[5] has prompted us to develop several connective methodologies

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(1) Ward, A.; Campoli-Richards, D. M. *Drugs* **1986**, *32*, 425.
(2) Chain, E. B.; Mellows, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 294.
(3) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 561.
(4) (a) All references cited in: DeShong, P.; Class, Y. L. *Chem. Rev.* **1995**, 1843. (b) Balog, A.; Yu, M. S.; Curran, D. P. *Synth. Commun.* **1996**, *26*, 935. (c) McKay, C.; Simpson, T. J.; Willis, C. L.; O'Hanlon, P. J.; Forest, A. K. *Chem. Commun.* **2000**, 1109. For synthetic approaches, see: (d) Khan, N.; Xiao, H.; Zhang, B.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303. (e) Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529. (f) Honda, T.; Kimura, N. *Org. Lett.* **2002**, *4*, 4567.
(5) (a) Markó, I. E.; Plancher, J. M. *Tetrahedron Lett.* **1999**, *40*, 5465. (b) Leroy, B.; Markó, I. E. *Tetrahedron Lett.* **2001**, *42*, 8685. (c) Leroy, B.; Markó, I. E. *J. Org. Chem.* **2002**, *67*, 8744. (d) Dubost, C.; Markó, I.E.; Bryans, J. *Tetrahedron Lett.* **2005**, *46*,4005.

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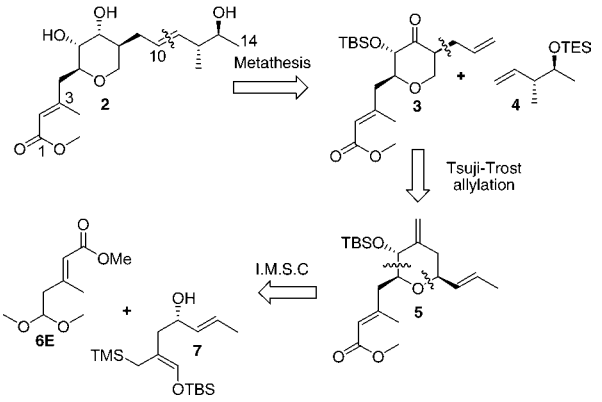
for the stereocontrolled preparation of polysubstituted tetrahydropyrans.[6] In this regard, the preparation of methyl monate C **2**, the methyl ester derivative of pseudomonic acid C **1**, attracted our attention. In this paper, we wish to report the successful asymmetric synthesis of compound **2**.

Our retrosynthetic analysis is displayed in Scheme 1. Cleavage of the C10−C11 olefinic linkage led to two

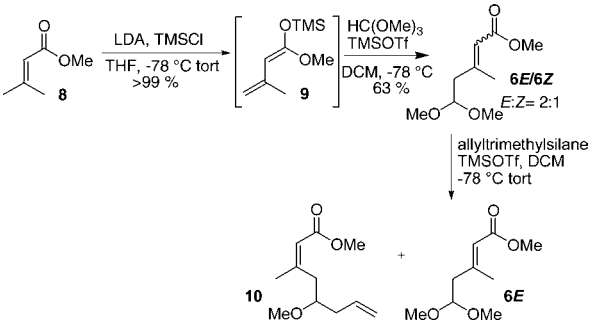
Scheme 1. Retrosynthesis



fragments: pyran **3** and the functionalized side chain **4**. Retro-Tsuji−Trost allylation, followed by adjustment of the functionalization around the heterocyclic nucleus, delivered ester **5** which would originate from the union of the optically active alcohol **7** with acetal **6*E*** (Scheme 1).

Our synthesis begins with the preparation of acetal **6*E*** using a Mukaiyama-type condensation.[7] The acrylic ester **8** was initially converted quantitatively into the corresponding silyl enol ether **9**,[8] which was subsequently condensed with trimethyl orthoformate in the presence of TMSOTf. Although the reaction proceeded smoothly in 63% yield, a mixture of the two double bond isomers **6*E*** and **6*Z*** was obtained in a ratio of 2:1 (Scheme 2).

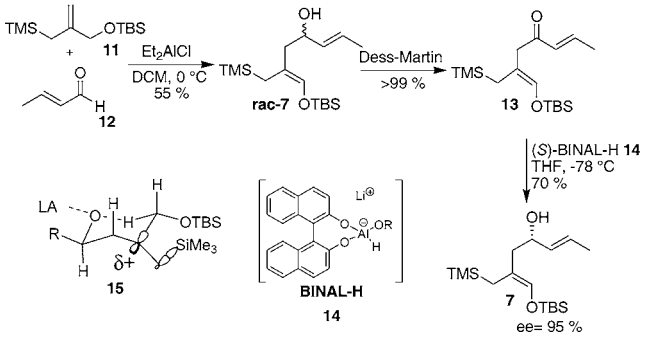
Scheme 2



Unfortunately, the separation of these two diastereoisomers proved to be impossible by liquid chromatography. However, preliminary studies indicated that the (*Z*) isomer was more reactive than its (*E*) counterpart under appropriate conditions. Accordingly, when a 2:1 mixture of **6*E*** and **6*Z*** was reacted with allyltrimethylsilane (0.33 equiv) in the presence of TMSOTf (0.33 or 1 equiv compared to **6*Z***), smooth disappearance of the (*Z*) isomer was observed. The (*E*)-configured derivative remained unaffected. After workup and MPLC separation, **6*E*** could be recovered (Scheme 2).

This convenient procedure allowed us to secure an easy access to geometrically pure **6*E*** in 42% overall yield and to focus our efforts on the preparation of the optically active fragment **7**. The ene reaction between the readily available allylsilane[9] **11** and crotonaldehyde **12**, in the presence of 1.5 equiv of Et_2AlCl, produced the allylic alcohol **rac-7** in 55% yield (Scheme 3). It is interesting to note that only the (*Z*)-

Scheme 3

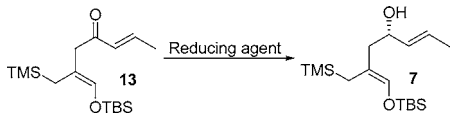


silylenol ether is formed during this reaction. This selectivity probably originates[10] from the involvment of the cyclic transition state **15** in which the partial positive charge is stabilized by the β-effect of the silicon substituent and all the steric interactions are minimized.

In the context of an enantioselective synthesis, racemate **7** has to be resolved. Kinetic resolution using a variety of methods, including the enzyme PS Amano Lipase,[11] was initially attempted, but either poor yields or no separation at all was observed. Moreover, the prospect of losing at least 50% of the rather precious annelating agent **7** prompted us to consider alternative pathways. Thus, it was decided to oxidize the substrate to the corresponding ketone and perform an asymmetric reduction. This route was selected, even though we were acutely aware of the possible instability of enone **13**. In the event, treatment of **rac-7** with the Dess−Martin periodinane afforded smoothly and quantitatively the prochiral ketone **13** which proved to be more stable than anticipated. Having established a ready access to **13**, we next turned our attention to its enantioselective reduction. Some selected results are displayed in Table 1. Various oxazaboro-

(6) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595.
(7) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1975**, *97*, 7503.
(8) Used without purification.
(9) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.
(10) Markó, I. E.; Dumeunier, R.; Leclercq, C.; Leroy, B.; Plancher, J. M.; Mekhalfia, A.; Bayston, D. J. *Synthesis* **2002**, *7*, 958.
(11) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G. *J. Org. Chem.* **1987**, *52*, 256.

Table 1. Enantioselective Reduction of Enone **13**

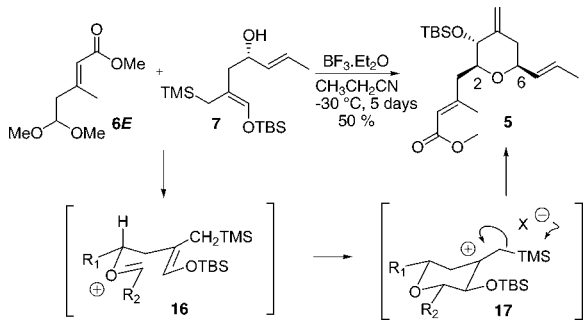


entry	reducing agent	yield (%)	ee (%)
1	CBS-Me(a)	71	24
2	CBS-Bu	70	83
3	Alpine-Borane	35	91
4	BINALH (R = Me)	60	30
5	BINALH (R = Et)	95	36
6	BINALH (R = iPr)	70	95

lidines[12] (entries 1 and 2) and Midland's Alpine boranes (entry 3)[13] were initially screened and gave encouraging results. However, the BINAL-H hydrides **14** developed by Noyori[14] proved to be the most efficient. Fine-tuning the bulkiness of the R group turned out to be of paramount importance in our case. Indeed, whereas the methyl and ethyl derivatives **14** (R = Me or Et, entries 4 and 5) only afforded low enantiomeric excesses (30% ee and 36% ee, respectively), the use of the isopropyl-containing reagent (entry 6) enabled us to produce **7** in 70% yield and 96% ee.[15]

With **6*E*** and the optically active alcohol **7** in hand, the time had come to assemble the cyclic core of methyl monate C **2**. These compounds were thus engaged in an intramolecular modified Sakurai cyclization (IMSC), an efficient methodology developed in our laboratory to construct functionalized pyran rings. Condensation of **6*E*** with **7**, promoted by $BF_3{\cdot}Et_2O$, provided the desired tetrahydropyran **5** in 50% yield. It is noteworthy that a single diastereoisomer, bearing a 2,6-*cis*-relationship and possessing an equatorially disposed OTBS group, has been produced (Scheme 4).

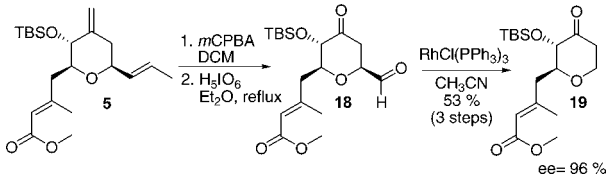
Scheme 4



This stereochemistry arises from the passage through the cyclic transition state **16**, in which all the substituents occupy a pseudo-equatorial position.

At this stage, the chemoselective ozonolysis of the two electron-rich alkenes was attempted, alas to no avail. However, treatment of substrate **5** with *m*-CPBA, at 0 °C, for 20 h, resulted in the smooth formation of a bis-epoxide.[16] Oxidative cleavage of the crude product by H_5IO_6 delivered the ketoaldehyde **18**. Decarbonylation of tetrahydropyran **18**, in the presence of Wilkinson's catalyst,[17] provided ketone **19** in 53% yield over three steps (Scheme 5).

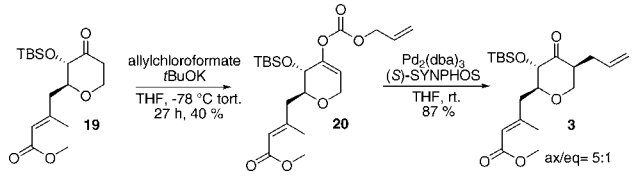
Scheme 5



At this stage, the enantiomeric purity of **19** was determined to be 96% by chiral GC.[18]

The conversion of **19** into the key intermediate **3** was next investigated. Preliminary model studies suggested that an asymmetric allylic alkylation[19] might be efficient in controlling the axial introduction of the side chain. Therefore, the reaction of ketone **19** with allyl chloroformate, in the presence of potassium *tert*-oxide, gave the sensitive allylcarbonate **20** which was directly submitted to the allylic rearrangement in the presence of $Pd_2(dba)_3$ and a chiral ligand. After extensive optimization, (*S*)-SYNPHOS proved to be the ligand of choice and THF the best solvent. Under these conditions, the desired adduct **3** was obtained in 87% yield as a 5:1 epimeric ratio in favor of the axial isomer (Scheme 6).[20]

Scheme 6

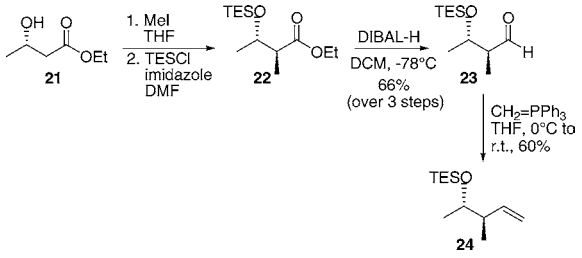


At this stage, the preparation of the C12−C15 side chain was accomplished from the commercially available β-hydroxy ester **21**. Thus, stereoselective methylation under the conditions of Fràter[21] followed by protection of the free

(12) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769.
(13) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(14) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishiwaza, A. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(15) The enantiomeric excess of ***7*** was determined by derivatisation with Naproxen followed by ^1H NMR analysis.
(16) No epoxydation of the α, β-unsaturated ester was observed under these conditions.
(17) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.
(18) G.C. conditions: 170 °C isotherm on a Chiraldex column (25 m × 0.25 mm × 0.25 μm).
(19) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
(20) Performing this allylation in dioxane afforded a 12/1 ax/eq ratio albeit in much reduced yield (24%).
(21) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.

hydroxyl group with a TES ether smoothly afforded compound **22**. Reduction of silyl ether **22** with DIBAL-H generated the corresponding aldehyde, which was converted into fragment **24** using a Wittig reaction (Scheme 7).

Scheme 7



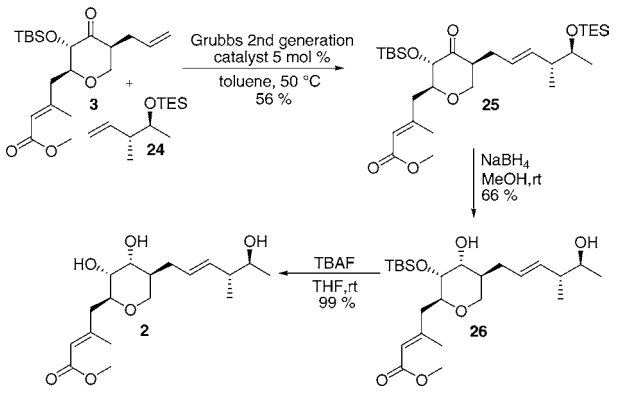
The complete side chain of methyl monate C **2** was introduced by a cross-metathesis[22] between **3** and **24**. Accordingly, a solution of both alkenes in toluene was treated with 5 mol % of the second-generation Grubbs' catalyst, at 50 °C, to furnished **25** in 56% yield. Remarkably, only the (*E*) isomer was formed (Scheme 8).

Introducing the last chiral center required a reduction of the ketone into the corresponding axial alcohol. Although problems were anticipated in the stereochemical outcome of this reaction, we were pleasantly surprised to note that treatment of **25** with sodium borohydride in MeOH at room temperature led to the desired axial isomer **26**, with concomitant deprotection of the triethylsilyl group, in 66% yield.

Finally, deprotection of the TBS ether was accomplished using 1 equiv of TBAF in THF, at room temperature, to give methyl monate C **2** quantitatively ($[\alpha]_D = +8.4$ ($c = 0.5$, $CHCl_3$)). The synthetic sample displayed spectral data in perfect agreement ($[\alpha]_D = +8.2$ ($c = 0.5$, $CHCl_3$)) with those of an authentic sample prepared according to Clayton et al.[23]

(22) Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

Scheme 8



In summary, the diastereo- and enantioselective total synthesis of methyl monate C **2** has been accomplished efficiently from readily available starting materials. Our approach, which is convergent and flexible, involves an ene-IMSC sequence to build the substituted pyran motif of this natural product, a highly stereoselective axial allylation and a cross-metathesis to install the full side chain.

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Supporting Information Available: Full spectral data and procedure for all intermediates. Copies of ^1H and ^{13}C NMR spectra for methyl monate C **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Clayton, P. J.; Rogers, N. H.; O'Hanlon P. J.; King T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827.