Tetrahedron Letters 50 (2009) 1504–1506

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective construction of substituted tetrahydropyrans using an intramolecular oxy-Michael strategy

Fumika Yakushiji [a], Jacques Maddaluno [b], Masahiro Yoshida [a], Kozo Shishido [a,*]

[a] Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan
[b] Laboratoire des Fonctions Azotées & Oxygènées Complexes de l'IRCOF, CNRS UMR 6014 & FR 3038, Université de Rouen, 76821 Mont St. Aignan, France

ARTICLE INFO

Article history:
Received 16 December 2008
Revised 14 January 2009
Accepted 15 January 2009
Available online 20 January 2009

ABSTRACT

The highly diastereoselective construction of substituted tetrahydropyrans, a common core segment (C3–C10) of the thiomarinols and the pseudomonic acid antibiotics, has been accomplished using the intramolecular oxy-Michael reaction under both basic and high-pressure conditions followed by regio- and stereoselective epoxide opening with acetylide.

Thiomarinols,[1] hybrid antibiotics composed of a pseudomonic acid analogue and a pyrrothine core,[2] and pseudomonic acids[3] belong to the family of C-glycopyranoside antibiotics. Produced by *Alteromonas rava* sp. nov. SANK 73390 and *Pseudomonas fluorescens*, respectively, these compounds possess potent antibiotic activities, in particular thiomarinol B, which showed excellent in vitro antimicrobial activity against Gram-positive and Gram-negative bacteria.[1c] Because of their intriguing structural features and interesting biological profiles, they represent attractive targets for total synthesis. Although many fascinating routes to pseudomonic acids[3] have been reported, so far only one successful, and elegant, total synthesis of thiomarinol antibiotic has been reported by Gao and Hall.[4]

During the course of our studies directed toward the total synthesis of thiomarinols A and B, we sought to develop an efficient methodology for the diastereoselective construction of the C3–C10 segment **1** containing the tetrahydropyran ring,[5] which is a common core structure of the thiomarinols and pseudomonic acids (Fig. 1).

The key feature of our strategy is the use of an intramolecular oxy-Michael (IMOM) reaction[6] of the hydroxy enoate **2** bearing a *cis*-epoxide for the construction of the tetrasubstituted tetrahydropyran **3a**. We anticipated that the presence of the *cis*-epoxide[6c] would promote the kinetic formation of the pyran ring by the Thorpe-Ingold-like effect.[7] The diastereoselectivity at the future C5 can be deduced by comparing the possible transition states T_1 and T_2, in which the sterically less demanding transition state T_1 might be predominant, and the pyran **3a** with the 5*S* configuration would be generated as the major product. The epoxide could then be opened by an acetylide anion at the future C8 in a regio- and stereoselective fashion resulting in the formation of the tetrasubstituted tetrahydropyran **1** with the requisite stereochemistry (Scheme 1).

In this Letter, we report the stereochemical outcome of the IMOM reaction of **2** under anionic and unprecedented high-pressure conditions[8] and the subsequent transformation of the cycloadducts **3** to the C3–C10 segment **1** of the antibiotics. Although many examples of carbon–carbon[9] and carbon–nitrogen bonds[10] forming intermolecular Michael reaction under high-pressure conditions have been reported, there are very few examples in the literature on the intramolecular version.[11]

The substrates for the IMOM reaction were synthesized as shown in Scheme 2. To determine the stereochemical outcome of

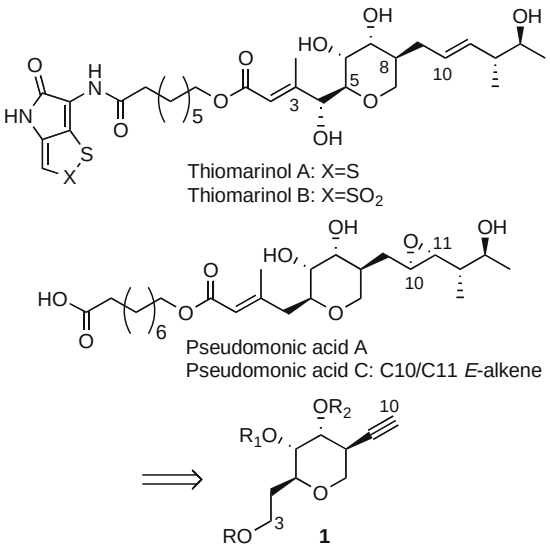

Figure 1. Thiomarinols and pseudomonic acids and the C3–C10 core segment.

* Corresponding author. Tel.: +81 88 6337287; fax: +81 88 6339575.
E-mail address: shishido@ph.tokushima-u.ac.jp (K. Shishido).

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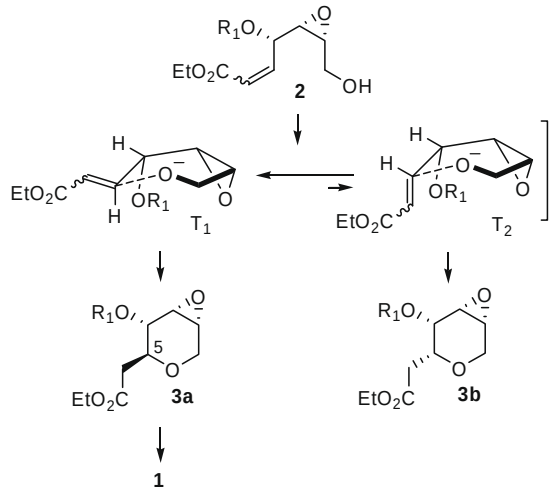
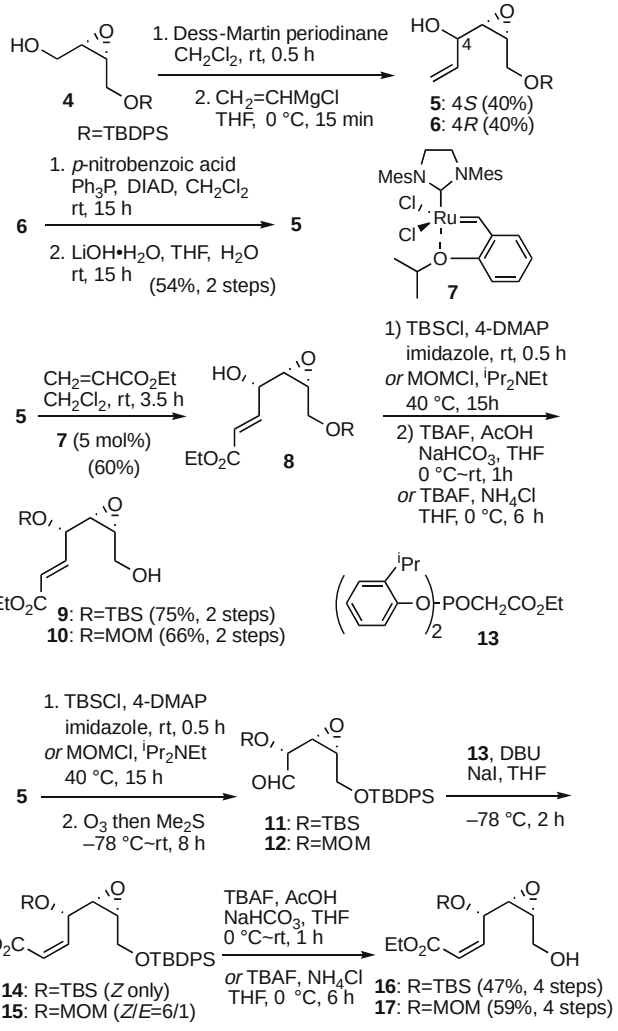
doi:10.1016/j.tetlet.2009.01.084



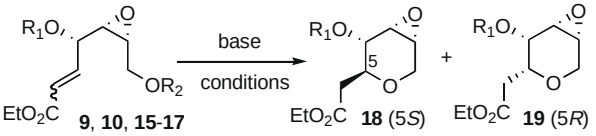
Scheme 1. Synthetic strategy.

the cyclization, we prepared the hydroxy *E*-enoates **9** and **10** and the *Z*-enoates **16** and **17**. Starting with the optically active epoxy alcohol **4**, oxidation and vinylation provided a chromatographically separable 1:1 mixture of the alcohols **5** and **6**. Conversion of the undesired 4*R*-isomer **6** to the desired 4*S*-isomer **5** could be carried out by the Mitsunobu reaction followed by hydrolysis. The allyl alcohol **5** was subjected to cross metathesis[12] with ethyl acrylate and the Hoveyda catalyst **7**[13] to provide the *E*-enoates **8**, which furnished **9** and **10** via silylation or methoxymethylation followed by selective desilylation.[14] The *Z*-enoates **16** and **17** were prepared starting from the aldehydes **11** and **12**, which were obtained by sequential protection of the hydroxyl function in **5** and by ozonolysis. Exposure of **11** and **12** to Ando olefination conditions[15] with **13** resulted in the exclusive formation of the *Z*-enoate **14** and a *Z*/*E* = 6:1 inseparable mixture of **15**, respectively. They were then converted to **16** (*Z* only) and **17** (*Z*/*E* = 6:1) by desilylation in good overall yields from **5** (Scheme 2).



Scheme 2. Synthesis of the substrates.

Table 1
IMOM reaction under basic conditions



Entry	Enoate (config.)	Base	Conditions	Yield (%)	**18**:**19**
1	**9** (*E*)	NaH	CH_2Cl_2,0 °C, 2 h	89	5.7:1
2	**10** (*E*)	NaH	CH_2Cl_2, 0 °C, 2 h	97	12:1
3	**16** (*Z*)	NaH	CH_2Cl_2, 0 °C, 2 h	90	>99:1
4	**17** (*Z*/*E* = 6:1)	NaH	CH_2Cl_2, 0 °C, 2 h	99	>99:1
5	**15** (*Z*/*E* = 6:1)	TBAF	THF, rt, 1 h	92	>99:1

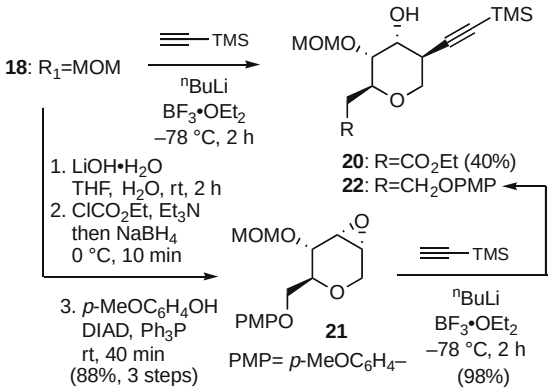
With the hydroxy enoates in hand, we initially examined the key IMOM reaction under basic conditions.[20] Treatment of the *E*-enoates **9** and **10** with NaH in dichloromethane (DCM) at 0 °C for 2 h provided a separable mixture of the diastereoisomers **18** (5*S*) and **19** (5*R*) in 89% yield (dr = 5.7:1; R_1 = TBS) and 97% yield (dr = 12:1; R_1 = MOM), respectively (Table 1, entries 1 and 2). It was demonstrated that the yield and diastereoselectivity were affected by changing the C4-hydroxy protective group (TBS→MOM) in the *E*-enoates **9** and **10**. When the reaction was conducted for the *Z*- and *Z*-rich (*Z*/*E* = 6:1) enoates **16** and **17** under the same reaction conditions, the desired pyran **18** was obtained as a single diastereomer in 90% (R_1 = TBS) and 99% yields (R_1 = MOM), respectively (Entries 3 and 4). One-pot conversion of **15** to **18** (a mixture of *Z*/*E* = 6:1) via a desilylation/cyclization sequence was carried out by treatment of **15** with TBAF in THF providing **18** (R_1 = MOM) in 92% yield (Table 1, entry 5).

Next, we examined the conversions under high-pressure conditions.[21] After considerable experimentation, it was found that the presence of Hünig's base ($^iPr_2NEt$) as an additive[16] was necessary. Thus, a solution of **9** in a mixture of $^iPr_2NEt$ and DCM (1/9) was exposed to the high-pressure conditions (12.6 kbar), and the diastereomeric pyrans **18** and **19** were obtained in 62% yield in a ratio of 4.6:1 (Table 2, entry 1). It should be noted that in the case of the *E*-enoate **9**, the addition of ethanol[17] to the reaction media increased the yield up to 96% with higher diastereoselectivity (16:1) (entry 2). As in the case under basic conditions, the *Z*-enoates **16** and **17** provided excellent yields and diastereoselectivity of the desired pyran **18** (entries 3 and 4). When the reaction was carried out at an atmospheric pressure, the starting hydroxy enoate was recovered completely (Table 2, entry 5).

Since attempted treatment of the epoxy pyran **18**[18] (R_1 = MOM) with trimethylsilylacetylene in the presence of ^nBuLi and boron trifluoride etherate[19] produced the acetylenic alcohol **20**[18] only in 40% yield, **18** (R_1 = MOM) was hydrolyzed and the resulting carboxylic acid was reduced via a mixed anhydride to give the expected alcohol which was immediately protected as the

Table 2
IMOM reaction under high-pressure conditions

Entry	Enoate (config.)	Pressure (kbar)	Conditions	Yield (%)	**18**:**19**
1	**9** (*E*)	12.6	$^{i}Pr_2NEt/CH_2Cl_2$ = 1/9, rt, 15 h	62	4.6:1
2	**9** (*E*)	10.9	$^{i}Pr_2NEt/CH_2Cl_2$/EtOH = 1/4.5/4.5, rt, 19 h	96	16:1
3	**16** (*Z*)	13.3	$^{i}Pr_2NEt/CH_2Cl_2$ = 1/9, rt, 19 h	96	>99:1
4	**17** (*Z*/*E* = 6:1)	12.9	$^{i}Pr_2NEt/CH_2Cl_2$ = 1/9 rt, 18 h	99	>99:1
5	**16** (*Z*)	—	$^{i}Pr_2NEt/CH_2Cl_2$ = 1/9, rt, 7 days	Recovered	



Scheme 3. Transformation of **18** to the C3–C10 segment **22**.

p-methoxyphenyl (PMP) ether using the Mitsunobu protocol to give **21** in 88% yield for the three steps. The latter was then treated under the same reaction conditions as for **18** to provide the pyran **22** with the requisite four contiguous stereogenic centers in excellent yield (Scheme 3).

In summary, an efficient protocol for the highly diastereoselective synthesis of the 2,3,4,5-tetrasubstituted tetrahydropyran core structure of the thiomarinols and pseudomonic acid antibiotics was devised with use of the IMOM reaction of the epoxy hydroxy *Z*-enoate under both basic and high-pressure conditions. It should be emphasized that this is the first time that the IMOM reaction for assembling the substituted tetrahydropyrans under high-pressure has been efficiently accomplished. Efforts aimed at completion of the total synthesis of thiomarinols are ongoing and will be reported in due course.

Acknowledgments

We thank Dr. Isabelle Chataigner of the Université de Rouen for technical assistance with high-pressure experiments and for helpful discussions. This work was supported financially in part by JSPS Research Fellowship for Young Scientists (to F.Y.) (No. 19•6569) and by a Grant-in-Aid for program for Promotion of Basic and Applied Researches for Innovations in Bio-oriented Industry.

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18. *Compound* **18**: Colorless oil. IR (neat) cm^{-1}: 2901, 1735, 1446, 1257, 1148, 1045, 914, 728; α_D^{27} −34.27 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.83 (1H, d, *J* = 6.8 Hz), 4.76 (1H, d, *J* = 6.8 Hz), 4.20–4.10 (2H, m), 4.05 (1H, dd, *J* = 13 and 4.0 Hz), 3.88 (1H, d, *J* = 13 Hz), 3.81–3.74 (2H, m), 3.56 (1H, d, *J* = 4.8 Hz), 3.48 (1H, dd, *J* = 4.4 and 3.6 Hz), 3.45 (3H, s), 2.73 (1H, dd, *J* = 15 and 2.8 Hz), 2.39 (1H, dd, *J* = 15 and 7.2 Hz), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87 (s), 96.43 (t), 75.15 (d), 69.95 (d), 64.71 (t), 60.49 (t), 55.67 (d), 52.40 (d), 55.05 (q), 37.35 (t), 14.10 (q); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{18}O_6Na$ $[M+Na]^+$ 269.1001, found 269.1004. *Compound* **20**: Colorless oil. IR (neat) cm^{-1}: 3576, 2960, 2255, 2171, 1730, 1250, 1107, 1027, 844; α_D^{27} +39.02 (*c* 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.75 (1H, d, *J* = 6.8 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 4.22–4.12 (3H, m), 4.07 (1H, dt, *J* = 8.8 and 3.6 Hz), 3.89 (1H, dd, *J* = 11 and 2.8 Hz), 3.72 (2H, dd, *J* = 9.2 and 2.8 Hz), 3.43 (3H, s), 2.85 (1H, m), 2.71 (1H, dd, *J* = 15 and 4.0 Hz), 2.54 (1H, br s), 2.50 (1H, dd, *J* = 15 and 8.8 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 0.15 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.31 (s), 104.49 (d), 96.26 (t), 87.80 (d), 75.76 (d), 71.45 (d), 68.23 (d), 64.77 (t), 60.57 (t), 56.24 (q), 37.51 (t), 35.21 (d), 14.18 (q), 0.00 (t) × 3; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}O_6NaSi$ $[M+Na]^+$ 367.1553, found 367.1566.
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20. *General procedure for the IMOM reaction under anionic conditions*: To a solution (0.05 M) of NaH (2.5 equiv) in CH_2Cl_2 was added the hydroxy enoate (1 equiv) at 0 °C and was stirred at the same temperature for 2 h. The reaction mixture was quenched with satd $NaHCO_3$ (aq). The aqueous layer was extracted with AcOEt, and the extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified through silica gel column chromatography to give the cyclized product.
21. *General procedure for the IMOM reaction under high-pressure conditions*: A solution (0.05 M) of the hydroxy enoate (1 equiv) in a mixture of $^{i}Pr_2NEt$ and the solvent (1:9) was allowed to stand under high pressure at room temperature for 15–19 h. After reversion to atmospheric pressure, the solvent was evaporated. The residue was purified through silica gel column chromatography to give the cyclized product.