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	A B S T R A C T
Article history: Received 16 December 2008 Revised 14 January 2009 Accepted 15 January 2009 Available online 20 January 2009	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 intra- molecular oxy-Michael reaction under both basic and high-pressure conditions followed by regio- and stereoselective epoxide opening with acetylide.

© 2009 Elsevier Ltd. All rights reserved.

Thiomarinols,¹ hybrid antibiotics composed of a pseudomonic acid analogue and a pyrrothine core,² and pseudomonic acids³ 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 Gramnegative 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 acids³ 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) reaction⁶ 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 T₁ and T₂, in which the sterically less demanding transition state T₁ 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 conditions⁸ and the subsequent transformation of the cycloadducts **3** to the C3–C10 segment **1** of the antibiotics. Although many examples of carbon–carbon⁹ and carbon–nitrogen bonds¹⁰ 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).

^{0040-4039/\$ -} see front matter \odot 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2009.01.084

4

5



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



Scheme 2. Synthesis of the substrates.

Table 1

17 (Z/E = 6:1)

15 (Z/E = 6:1)



THF, rt, 1 h

NaH

TBAF

undesired 4R-isomer 6 to the desired 4S-isomer 5 could be carried out by the Mitsunobu reaction followed by hydrolysis. The allyl alcohol 5 was subjected to cross metathesis¹² with ethyl acrylate and the Hoveyda catalyst 7^{13} to provide the *E*-enoates **8**, which furnished 9 and 10 via silulation 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 conditions¹⁵ 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).

With the hydroxy enoates in hand, we initially examined the key IMOM reaction under basic conditions.²⁰ Treatment of the Eenoates 9 and 10 with NaH in dichloromethane (DCM) at 0 °C for 2 h provided a separable mixture of the diastereoisomers **18** (5S) 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 vield and diastereoselectivity were affected by changing the C4-hydroxy protective group (TBS \rightarrow 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 (ⁱPr₂NEt) as an additive¹⁶ was necessary. Thus, a solution of **9** in a mixture of ${}^{i}Pr_{2}NEt$ 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 $\mathbf{9}$, the addition of ethanol¹⁷ 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} (R₁ = MOM) with trimethylsilylacetylene in the presence of ⁿBuLi and boron trifluoride etherate¹⁹ 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

>99:1

>99:1

99

92

Table 2		
IMOM reaction under	high-pressure	conditions

Entry	Enoate (config.)	Pressure (kbar)	Conditions	Yield (%)	18:19
1	9 (E)	12.6	ⁱ Pr ₂ NEt/CH ₂ Cl ₂ = 1/9, rt, 15 h	62	4.6:1
2	9 (E)	10.9	$^{i}Pr_{2}NEt/CH_{2}Cl_{2}/EtOH = 1/4.5/4.5, rt, 19 h$	96	16:1
3	16 (<i>Z</i>)	13.3	$^{i}Pr_{2}NEt/CH_{2}Cl_{2} = 1/9$, rt, 19 h	96	>99:1
4	17 $(Z/E = 6:1)$	12.9	$^{i}Pr_{2}NEt/CH_{2}Cl_{2} = 1/9 \text{ rt}, 18 \text{ h}$	99	>99:1
5	16 (<i>Z</i>)	-	$^{i}Pr_{2}NEt/CH_{2}Cl_{2} = 1/9$, 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.

References and notes

- (a) Shiozawa, H.; Kagasaki, T.; Kinoshita, T.; Haruyama, H.; Domon, H.; Utsui, Y.; Kodama, K.; Takahashi, S. J. Antibiot. 1993, 46, 1834; (b) Shiozawa, H.; Takahashi, S. J. Antibiot. 1994, 47, 851; (c) Shiozawa, H.; Kagasaki, T.; Torikawa, A.; Tanaka, N.; Fujimoto, K.; Hata, T.; Furukawa, Y.; Takahashi, S. J. Antibiot. 1995, 48, 907.
- (a) Ettinger, L.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Kardolfer, F.; Neipp, L.; Prelog, V.; Zähner, H. *Helv. Chim. Acta* **1959**, *42*, 563; (b) Celmer, W. D.; Solomons, I. A. J. Am. Chem. Soc. **1955**, 77, 2861.
- 3. For a review, see: Class, Y. J.; DeShong, P. Chem. Rev. 1995, 95, 1843.
- 4. Gao, X.; Hall, D. G. J. Am. Chem. Soc. 2005, 127, 1628.
- 5. For a review, see: Clarke, P. A.; Santos, S. Eur. J. Org. Chem. 2006, 2045.

- For a review, see: (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545; (b) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. J. Am. *Chem. Soc.* **2000**, *122*, 5216; (c) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 2611; (d) Li, D. R.; Murugan, A.; Falck, J. R. J. Am. *Chem. Soc.* **2008**, *130*, 46. and references cited therein.
- (a) Eliel, E. L.; Wilen, S. H. Stereochemistry of Organic Compounds; Wiley: New York, 1994; (b) Jung, M. E.; Piizzi, G. Chem. Rev. 2005, 105, 1735.
- (a) Isaacs, N. S. In Liquid-Phase High Pressure Chemistry; John Wiley and Sons: Chichester, New York, Brisbane, Tronto, 1984; pp 182–201; (b) VanEldik, R.; Asano, T.; Le Noble, W. J. Chem. Rev. 1989, 89, 549; (c) Klärner, F. G.; Ruster, V.; Zimny, B.; Hochstrate, D. High-Pressure Res. 1991, 7, 133; (d) Matsumoto, K.; Hamana, H.; lida, H. Helv. Chim. Acta 2005, 88, 2033.
- (a) Uchida, T.; Matsumoto, K. Chem. Lett. **1981**, 1673; (b) Bunce, A. R.; Schlecht, F. M.; Dauben, G. W.; Heathcock, C. H. Tetrahedron Lett. **1983**, 24, 4943; (c) Dauben, G. W.; Gerdes, M. J. Tetrahedron Lett. **1983**, 24, 3841; (d) Dauben, G. W.; Bunce, A. R. J. Org. Chem. **1983**, 48, 4642; (e) Kotsuki, H.; Arimura, K. Tetrahedron Lett. **1997**, 38, 7583; (f) Jenner, G. New J. Chem. **1999**, 23, 525; (g) Camara, C.; Joseph, O.; Dumas, F.; d'Angelo, J.; Chiaroni, A. Tetrahedron Lett. **2002**, 43, 1445; (h) Knappwost-Gieseke, C.; Nerenz, F.; Wartchow, R.; Winterfeldt, E. Chem. Eur. J. **2003**, 9, 3849.
- (a) d'Angelo, J.; Maddaluno, J. J. Am. Chem. Soc. 1986, 108, 8112; (b) Dumas, F.; Fressigné, C.; Langlet, J.; Giessner-Prettre, C. J. Org. Chem. 1999, 64, 4725.
- It has been reported that the enolate anion, generated in situ, added to the βcarbon of butenolide intramolecularly under high-pressure conditions.^{9h}
- 12. Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. Pure Appl. Chem. 2002, 74, 7.
- 13. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2000, 122, 8168.
- Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. Synlett 2000, 1306.
- 15. Ando, K. J. Org. Chem. 1998, 63, 8411.
- Reactions of 9 and 16 under high-pressure conditions in the presence of other bases/solvents (Et₃N/CH₂Cl₂, Et₃N/THF, (-)-quinine/CH₂Cl₂, and diphenylguanidine/trifluorotoluene) led to lower yields and poor diastereoselectivities.
- 17. Al-Badri, H.; Maddaluno, J.; Masson, S.; Collignon, N. J. Chem. Soc., Perkin Trans. 1 **1999**, 2255.
- Compound **18**: Colorless oil. IR (neat) cm⁻¹: 2901, 1735, 1446, 1257, 1148, 1045, 914, 728; $\alpha_{\rm D}^{27}$ –34.27 (c 1.07, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 4.83 18 (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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₁₈O₆Na [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, CHCl₃); ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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) \times 3; HRMS (ESI) m/z calcd for C16H28O6NaSi [M+Na]+ 367.1553, found 367.1566.
- (a) Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron* **1984**, 45, 9265; (b) Shindo, M.; Sugioka, T.; Shishido, K. *Tetrahedron Lett.* **2004**, 49, 9265.
- 20. General procedure for the IMOM reaction under anionic conditions: To a solution (0.05 M) of NaH (2.5 equiv) in CH₂Cl₂ 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 NaHCO₃ (aq). The aqueous layer was extracted with AcOEt, and the extract was washed with brine, dried over MgSO₄, 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 ${}^{1}\text{Pr}_2\text{NEt}$ 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.