Stereoselective Synthesis of the Chiral Tetrahydropyrane Core of Swinholides and Misakinolides

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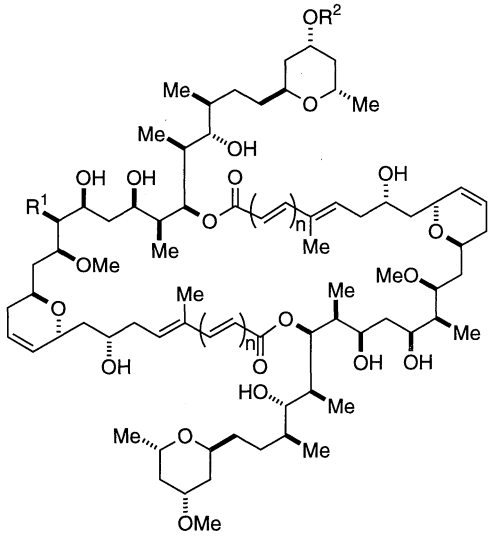
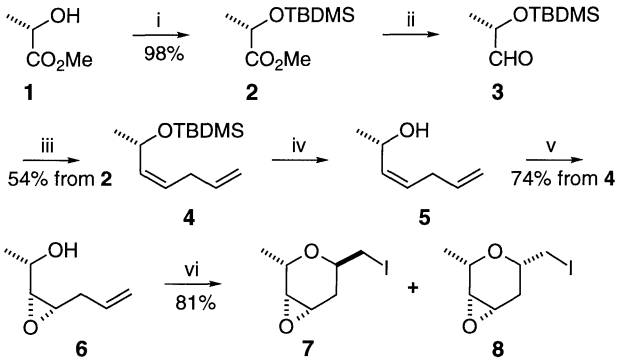
Stereoselective synthesis of the optically pure tetrahydropyrane core of swinholides and misakinolide A starting from (*S*)-methyl lactate is described in which the highly stereoselective intramolecular iodoetherification for construction of the tetrahydropyrane ring and the regioselective ring-opening reaction of an epoxide are involved as key steps.

The marine natural products swinholides A, B and C, 44-membered dimeric macrolides, isolated from the Okinawan marine sponge *Theonella swinhoei*,[1] and misakinolide A, a 40-membered dimeric lactone, isolated from another Okinawan marine sponge *Theonella*,[2] have been revealed to exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity.[1-3] The stereostructures of the monomeric units of swinholide A and misakinolide A are remarkably similar one another and only the number of double bond connected to a carboxyl group is different. The structures of these families are characterized by the *C2*-symmetrical dimeric macrolides in which two polypropionate-derived chains including a gigantic lactone ring take axial orientation on a tetrahydropyrane ring. Their unique structures and potent anticancer activities have elicited much attention from synthetic organic chemists.[4,5] As part of our synthetic studies toward the polypropionate-derived bioactive compounds possessing characteristic sequences of alternating methyl- and hydroxyl-substituted carbons,[6] we set about asymmetric total synthesis of the swinholide family. We report here the stereoselective synthesis of the common tetrahydropyrane core of swinholides and misakinolide A starting from methyl (*S*)-lactate which involves the highly stereoselective intramolecular iodoetherification for construction of the tetrahydropyrane ring and the regioselective ring-opening reaction of an epoxide as key steps.



Swinholide A: n=1, R^1=R^2=Me
Swinholide B: n=1, R^1=H, R^2=Me
Swinholide C: n=1, R^1=Me, R^2=H
Misakinolide A: n=0, R^1=R^2=Me



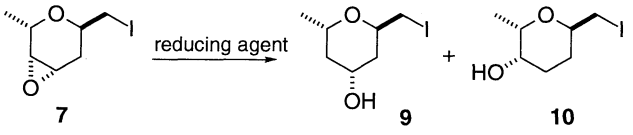
Scheme 1. Reagents and conditions: i. TBDMSCl, imidazole, CH_2Cl_2, 0 °C; ii. DIBAL-H, toluene, -78 °C; iii. 3-butenyltriphenylphosphonium bromide, BuLi, toluene; iv. TBAF, THF; v. MCPBA, CH_2Cl_2, 0 °C; vi. I[(coll)$_2$ClO$_4$], CH_2Cl_2, 0 °C.

The starting methyl (*S*)-lactate **1** was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in CH_2Cl_2 to give **2**[7] in nearly quantitative yield (Scheme 1). Reduction of **2** with DIBAL-H in toluene cleanly produced the aldehyde **3**[7] which was subjected to the Wittig reaction with 3-butenyltriphenylphosphonium bromide in toluene to give the (*Z*)-alkene **4** as a single product in 54% yield for the two steps. After removal of the TBDMS group of **4** with Bu_4NF (TBAF) in THF, the resulting (*Z*)-allylic alcohol **5** was treated with MCPBA in CH_2Cl_2 to afford a 94 : 6 mixture of the α-epoxy alcohol **6** and its β-isomer in 74% overall yield.[8] In turn, the epoxides were subjected to the intramolecular haloetherification, the key reaction in the present synthesis, aiming at the stereospecific construction of the tetrahydropyrane ring bearing an axial halomethyl substituent. However, the reaction of **6** with NBS or NIS was found to be fruitless under various conditions since the former reactions resulted in the predominant formation of bromohydrins at the vinyl portion, while the latter reaction was extremely sluggish. Finally, we found that iodonium di-*sym*-collidine perchlorate I[(coll)$_2$ClO$_4$] discovered by Lemieux[9] served our purpose. Thus treatment of **6** with I[(coll)$_2$ClO$_4$] in CH_2Cl_2 at 0 °C afforded a 5 : 1 mixture of **7** : **8** in 81% yield after purification by silica gel chromatography. However, the stereochemistry of the product **7** could not be unambigously determined at this stage. Therefore the rigorous stereostructure of the cyclization product was determined after an epoxide-opening reaction.

The crucial epoxide-opening reaction of **7** was investigated

under various conditions. The results are summarized in Table 1. In consequence, reducing agents such as lithium aluminum hydride, lithium triethylborohydride, and lithium tri-*sec*-butylborohydride (L-Selectride) were found to be useless (entries 1-3). On the other hand, reduction with sodium cyanoborohydride ($NaBH_3CN$) smoothly proceeded in THF at 0 °C in the presence of $BF_3{\cdot}Et_2O$, giving a 3 : 2 mixture of **9** and **10** in 88% combined yield (entry 4). Soon, we found that DIBAL-H was a reagent of choice and investigated reduction of **7** with DIBAL-H in detail. At first, the reaction of **7** with DIBAL-H (2 equiv.) in CH_2Cl_2 at -78 °C produced a 4 : 1 mixture of **9** and **10** in 76% yield (entry 5). In turn, we examined the effect of an additive in the reaction and fortunately found that ethereal compounds as additive could considerably improve the ratio of **9** and **10** (entries 7-10). Eventually, the reaction in the presence of 1 equiv. of diethylether in CH_2Cl_2 at -94 °C gave the best result (entry 10) by which the ratio of **9** and **10** was improved up to 87 : 13. At this stage, the stereostructure of the major product **9** including the absolute structure has been unequivocally established by X-ray analysis (Figure 1). As shown in the ortep drawing, an iodomethyl group in **9** takes the axial orientation as expected. These results demonstrate that the intramolecular etherification of **6** by $I[(coll)_2ClO_4]$ occurred stereoselectively giving rise to **7**. The tetrahydropyranyl alcohol **9** thus obtained was successfully converted to the target molecule by methylation

Table 1. Epoxide ring-opening reaction of **7**



7 **9** **10**

Entry	Reagent(s)	Solvent	Temp./°C	Yield /%	Ratio of **9** and **10**
1	$LiAlH_4$	Et_2O	0	— [a]	
2	$LiB(C_2H_5)_3H$	THF	-20	— [a]	
3	L-Selectride	THF	-78	— [b]	
4	$NaBH_3CN$ $BF_3{\cdot}Et_2O$	THF	0	88	60 : 40
5	DIBAL-H	CH_2Cl_2	-78	76	80 : 20
6	DIBAL-H THF (1 eq)	CH_2Cl_2	-78	— [b]	
7	DIBAL-H $^iPr_2O$(1 eq)	CH_2Cl_2	-78	69	79 : 21
8	DIBAL-H Et_2O(1 eq)	CH_2Cl_2	-78	73	85 : 15
9	DIBAL-H DME (1 eq)	CH_2Cl_2	-94	77	86 : 14
10	DIBAL-H Et_2O(1 eq)	CH_2Cl_2	-94	78	87 : 13

[a] Complex mixture. [b] No reaction.

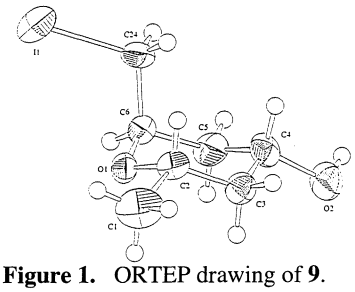


Figure 1. ORTEP drawing of **9**.

with trimethyloxonium tetrafluoroborate and proton sponge[10] in ether in 80% yield, though the *O*-methylation of **9** under usual basic conditions such as NaH/MeI and KH/MeI only resulted in decomposition of the substrate.

In summary, we have established a new and stereoselective synthetic route to the chiral tetrahydropyrane core of the swinholide family starting from (*S*)-methyl lactate, not by the use of sugar templates.

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References and Notes

1 S. Carmely and Y. Cashman, *Tetrahedron Lett.*, **26**, 511 (1985); M. Kobayashi, J. Tanaka, T. Katori, M. Matsuura, and I. Kitagawa, *Tetrahedron Lett.*, **30**, 2963 (1989); I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, J. Tanaka, M. Doi, and T. Ishida, *J. Am. Chem. Soc.*, **112**, 3710 (1990).
2 J. Tanaka, T. Higa, M. Kobayashi, and I. Kitagawa, *Chem. Pharm. Bull.*, **38**, 2967 (1990).
3 M. Doi, T. Ishida, M. Kobayashi, and I. Kitagawa, *J. Org. Chem.*, **56**, 3629 (1991).
4 I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, and J. D. Smith, *J. Am. Chem. Soc.*, **116**, 9391 (1994); A. P. Patron, P. K. Richter, M. J. Tomaszewski, R. A. Miller, and K. C. Nicolaou, *J. Chem. Soc., Chem. Commun.*, **1994**, 1147; P. K. Richter, M. J. Tomaszewski, R. A. Miller, A. P. Patron, and K. C. Nicolaou, *J. Chem. Soc., Chem. Commun.*, **1994**, 1151; T. Nakata, T. Komatsu, K. Nagasawa, H. Yamada, and T. Takahashi, *Tetrahedron Lett.*, **35**, 8225 (1994); T. Nakata, T. Komatsu, and K. Nagasawa, *Chem. Pharm. Bull.*, **42**, 2403 (1994); I. Paterson, J. G. Cumming, R. A. Ward, and S. Lamboley, *Tetrahedron*, **51**, 9393 (1995); I. Paterson, J. D. Smith, and R. A. Ward, *Tetrahedron*, **51**, 9413 (1995); I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, and K.-S. Yeung, *Tetrahedron*, **51**, 9437 (1995); I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, and S. Lamboley, *Tetrahedron*, **51**, 9467 (1995).
5 I. Paterson, K.-S. Yeung, C. Watson, R. A. Ward, and P. A. Wallace, *Tetrahedron*, **54**, 11935 (1998); I. Paterson, C. Watson, K.-S. Yeung, R. A. Ward, and P. A. Wallace, *Tetrahedron*, **54**, 11955 (1998).
6 M. Miyashita, M. Hoshino, and A. Yoshikoshi, *J. Org. Chem.*, **56**, 6483 (1991); T. Shiratani, K. Kimura, K. Yoshihara, S. Hatakeyama, H. Irie, and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, **1996**, 21; M. Miyashita, T. Shiratani, K. Kawamine, S. Hatakeyama, and H. Irie, *J. Chem. Soc., Chem. Commun.*, **1996**, 1027.
7 H. Hayakawa, M. Ohmori, K. Takamichi, F. Matsuda, and M. Miyashita, *J. Chem. Soc., Chem. Commun.*, **1997**, 1219.
8 B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, **1979**, 4733.
9 R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2190 (1965).
10 M. J. Diem, D. F. Burow, and J. L. Fry, *J. Org. Chem.*, **42**, 1801 (1977).