ORGANIC LETTERS

2000
Vol. 2, No. 14
2031−2034

A Stereoselective Synthesis of the C-10 to C-18 (Right-Half) Fragment of Mycalamides Employing Lewis Acid Promoted Intermolecular Aldol Reaction

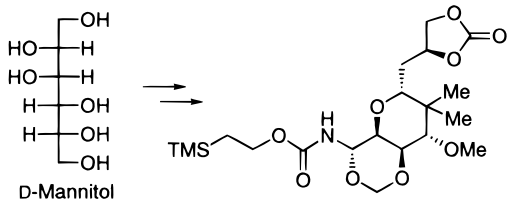
Masahiro Toyota,* Masako Hirota, Hitomi Hirano, and Masataka Ihara*

Department of Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai, 980-8578, Japan

mihara@mail.pharm.tohoku.ac.jp

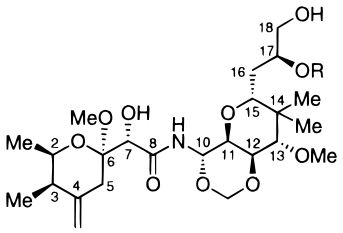
Received April 3, 2000

ABSTRACT



Beginning with D-mannitol, a stereoselective synthesis of the right-half segment of the mycalamides has been accomplished by employing Lewis acid catalyzed intermolecular aldol reaction and oxypalladation as the key steps.

Mycalamides A (**1**)[1] and B (**2**),[2] isolated from a New Zealand sponge of the genus *Mycale*, are potent antiviral and antitumor compounds (Figure 1).[3] On top of that, mycalamides A (**1**) and B (**2**) show strong immunosuppressive activity.[4] The mycalamides are structurally related to onnamides[5] and theopederins[6] and have a highly functionalized system in which an *exo*-olefinic tetrahydropyran connects with a trioxa-*cis*-decalin ring through a hydroxyacetamide moiety. The unique structural features of the mycalamides coupled with their biological properties have provided motivation for the development of synthetic strategies toward these marine natural products.[7] Herein we would like to present a stereoselective synthesis of the right segment (C-10 to C-18) of the mycalamides.



Mycalamide A (1): R=H
Mycalamide B (2): R=Me

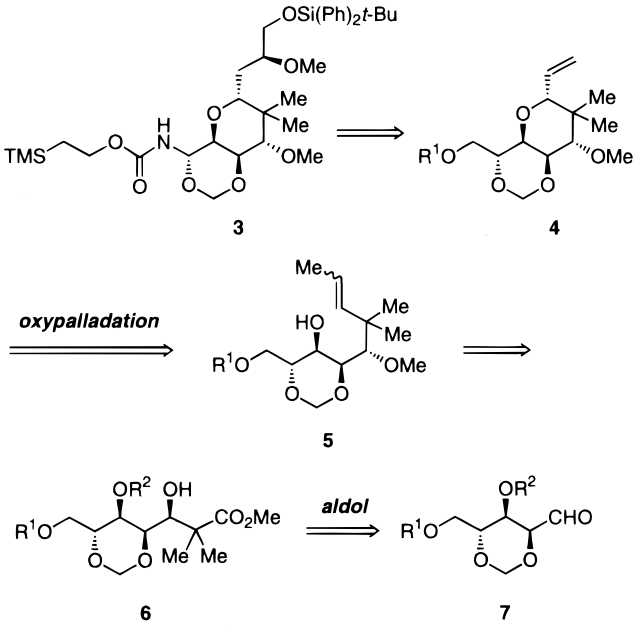
Figure 1.

(1) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc*. **1988**, *110*, 4850.
(2) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem*. **1990**, *55*, 223.
(3) (a) Burres, N. S.; Clement, J. J. *Cancer Res*. **1989**, *49*, 2935. (b) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull*. **1991**, *39*, 2152.
(4) Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser. H. *Eur. J. Immunol*. **1993**, *23*, 283.
(5) (a) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc*. **1988**, *110*, 4852. (b) Matsunaga, S.; Fusetani, N.; Nakano, Y. *Tetrahedron* **1992**, *48*, 8369.
(6) (a) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem*. **1992**, *57*, 3828. (b) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. *Tetrahedron* **1999**, *55*, 13697.
(7) **Total syntheses of the mycalamides:** (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem*. **1990**, *55*, 4242. (b) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett*. **1994**, *35*, 8229. (c) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 869.

10.1021/ol000072v CCC: $19.00
Published on Web 06/17/2000

Our retrosynthetic analysis for the right segment, **3**, of the mycalamides is shown in Scheme 1. The first key reaction

Scheme 1. Retrosynthetic Analysis for Right Segment of Mycalamides

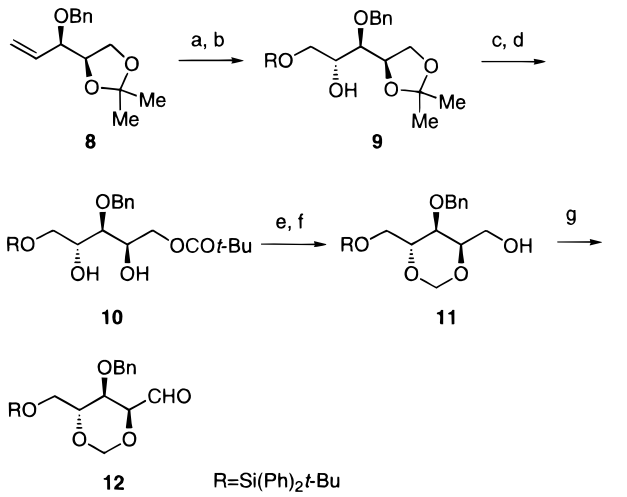


of the synthesis is the oxypalladation of **5** for the stereoselective construction of the trioxa-*cis*-decalin ring system **4**, which already has the right-half skeleton **3** of the mycalamides and suitable functionalities. A series of functional group modifications in **6** would lead to **5**. The second key step of the present synthesis is the Lewis acid promoted intermolecular aldol reaction of aldehyde **7** with dimethylketene methyl trimethylsilyl acetal.

The requisite aldehyde **12** for a Lewis acid promoted intermolecular aldol reaction was prepared in a stereoselective manner as depicted in Scheme 2. Thus, dihydroxylation of olefin **8**,[8] synthesized from D-mannitol, with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine oxide (1.5 equiv) afforded the corresponding diol (α: β = 8:1),[9] which was subjected to monosilylation to produce the desired α-alcohol **9** as a single stereoisomer after recrystallization. Hydrolysis of the acetal group of **9** followed by monoesterification with pivaloyl chloride furnished compound **10**, which was transformed into alcohol **11** by 1,3-dioxane formation[10] and DIBALH reduction of the pivaloate ester. Alcohol **11** was oxidized to aldehyde **12** without epimerization under Swern conditions.[11]

We initially investigated the intermolecular aldol reaction[12] of aldehyde **12** with the dimethylketene acetal in the presence

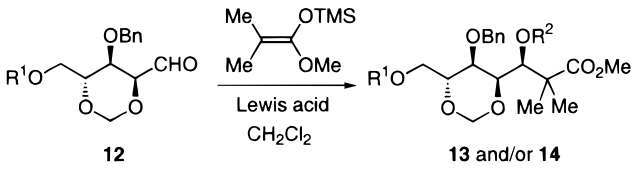
Scheme 2[a]



[a] Reagents and conditions: (a) OsO_4 (cat.), NMO (100%, α:β = 8:1); (b) *t*-Bu(Ph)$_2$SiCl, DMAP, Et_3N (51% after recrystallization); (c) AcOH−THF−H_2O (3:1:1), 55 °C (98%); (d) *t*-BuCOCl, pyridine (89%); (e) $(MeO)_2CH_2$, P_2O_5 (88%); (f) DIBALH, 0 °C (99%); (g) $(COCl)_2$, DMSO, Et_3N, −78 to −40 °C.

of 10 mol % of Yb(OTf)$_3$ (Table 1, entry 1). Under the above conditions, TMS ether **13** was obtained in 62% yield, as a major product, together with alcohol **14** (15% yield). When

Table 1. Lewis Acid Promoted Intermolecular Aldol Reaction[a]



entry	Lewis acid	equivalent	temp, °C	**13**, R^2 = TMS[b]	**14**, R^2 = H[b]	**12**[c]
1	Yb(OTf)$_3$	10 mol %	rt	62%	15%	
2	Sc(OTf)$_3$	10 mol %	−78 to rt		19%	19%
3	Cu(OTf)$_3$	10 mol %	rt		41%	25%
4	$InCl_3$	10 mol %	rt	41%	21%	
5	$TiCl_4$	150 mol %	−78		63%	

[a] R^1 = Si(Ph)$_2$*t*-Bu. [b] Yield for 2 steps from the alcohol **11**. [c] Recovered starting material.

Sc(OTf)$_3$ and Cu(OTf)$_2$ were used as Lewis acid, a considerable amount of the starting material **12** was recovered in addition to **14** (entries 2 and 3). Subjecting **12** to $InCl_3$ at room temperature led to the coupled products (**13** and **14**, with a combined yield greater than 60% yield, entry 4). Unlike the above results, only **14** was isolated when employing $TiCl_4$ as Lewis acid[13] (entry 5).

The stereochemistry of hydroxyester **14** was determined after the conversion of **14** to the bicyclic compound **19** as

(8) Nokami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181.
(9) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(10) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.
(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Review: Kobayashi, S. *Synlett* **1994**, 689.
(13) We evaluated Lewis acids such as TMSOTf, Eu(OTf)$_3$, Gd(OTf)$_3$, and Y(OTf)$_3$; however, all the Lewis acids tested gave low yields.

shown in Figure 3. The stereochemical outcome of the present aldol reaction might be rationalized by nucleophilic attack from less hindered face (Figure 2). With stereoselective

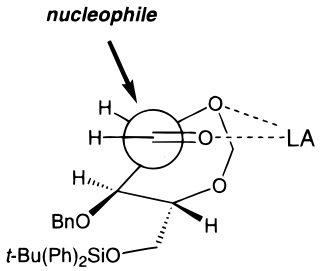
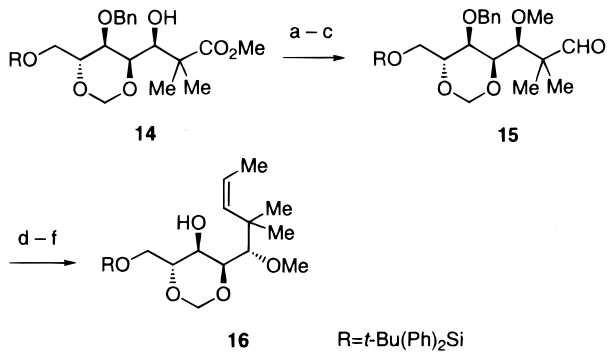


Figure 2.

induction of the side chain established, we next focused on the formation of the second ring of **4** (Scheme 1). The required substrate **16** for oxypalladation[14] was readily prepared via a six-step sequence from **14** (Scheme 3).

Scheme 3[a]

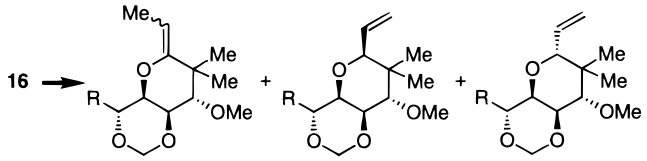


[a] Reagents and conditions: (a) NaH, MeI, 0 °C to rt (95%); (b) DIBALH, 0 °C (100%); (c) SO_3·Py DMSO, Et_3N (97%); (d) Ph_3PEtBr, BuLi, 0 °C (100%); (e) liquid NH_3, Li, −78 °C; (f) DDQ (73% for two steps).

Methylation of alcohol **14** followed by DIBALH reduction and oxidation provided aldehyde **15**, which was allowed to undergo a Wittig reaction to give the corresponding olefin. After reductive deprotection of the benzyl group, the phenyl moiety on the silicon, partially reduced, was reoxidized with DDQ to afford **16**.

Upon treatment of olefin **16** with $PdCl_2$ in the presence of CuCl in a mixture of DMF and water under a oxygen atmosphere, the oxypalladation proceeded smoothly, producing cyclized products (**17** and **18**), in 89% yield, as a 3:1 separable mixture (Table 2). The result from the next example was intriguing. Switching catalyst to $Pd(OAc)_2$[15]

Table 2. Intramolecular Oxypalladation of the Compound **16**[a]



entry	Pd	additive	solvent	17	18	19
1	$PdCl_2$	CuCl, O_2	DMF−H_2O	67%	22%	trace
2	$Pd(Oac)_2$		DMSO		84%	9%

[a] R = $CH_2OSi(Ph)_2t$-Bu.

led to **18** (84%) together with **19** (9%). The structures of **18** and **19** were confirmed by their NOE experiments as shown in Figure 3. Since the formation of the second ring proved

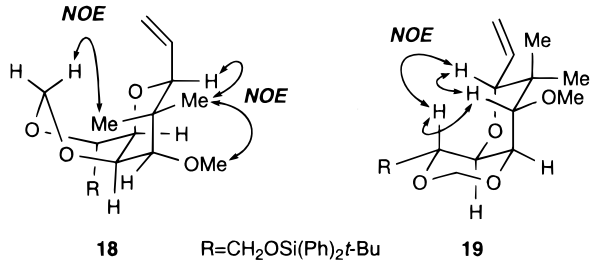


Figure 3.

to be more difficult than expected,[16] we decided to apply the experimental result (entry 1) of the oxypalladation of compound **16** to the construction of enol ether **17**. After transformation of **15** into the requisite substrate in three steps (74% overall yield), the oxypalladation was carried out under the reaction conditions similar to those of entry 1 (Table 2) to provide the desired enol ether **20** in 83% yield.

With the skeletal framework assembled, completion of the synthesis of the right segment of the mycalamides would require the installation of the side chain and the carbamate group. Compound **20** was subjected to ozonolysis followed by DIBALH reduction and acetylation, generating the corresponding lactol, which was exposed to allyltrimethylsilane in the presence of BF_3·Et_2O to give rise to the allylated trioxadecalin **21** as a single stereoisomer (Scheme 4).[17] Asymmetric dihydroxylation[18] of **21** gave a mixture of diol isomers (β: α = 3.6:1), which were easily separated after conversion to the cyclic carbonate with triphosgene. The major product was treated with tetrabutylammonium fluoride

(14) Review: Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49.

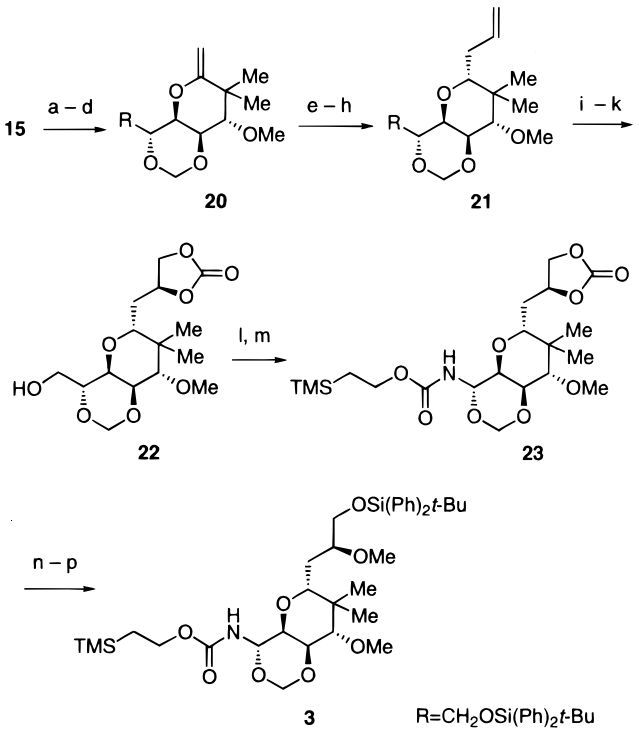
(15) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925.

(16) Although we tried to construct directly the second ring system of the right-half segment using **14** and **15**, the desired bicyclic compounds were not formed in considerable yield.

(17) Breitfelder, S.; Schlapbach, A.; Hoffmann, R. W. *Synthesis* **1998**, 468.

(18) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, B. *Chem. Rev* **1994**, *94*, 2483.

Scheme 4[a]



[a] Reagents and conditions: (a) Ph_3PMeBr, BuLi, 0 °C to rt (100%); (b) liquid NH_3, Li, −78 °C; (c) DDQ (74% for two steps); (d) $PdCl_2$, CuCl, O_2, DMF−H_2O (83%); (e) O_3, −78 °C, then Me_2S (80%); (f) DIBALH, −78 °C; (g) Ac_2O, pyridine (96% for two steps); (h) allyltrimethylsilane, BF_3·Et_2O, 4 Å molecular sieves, 0 °C; (i) K_2OsO_4·$2H_2O$, dihydroquinone 9-phenanthryl ether, $K_3Fe(CN)_6$, K_2CO_3 (96%, α:β = 1:3.6); (j) triphosgene, Et_3N (72%); (k) Bu_4NF (92%); (l) Jones reagent; (m) $(PhO)_2P(O)N_3$, Et_3N, 2-(trimethylsilyl)ethanol, 4 Å molecular sieves, 65 °C (70% for two steps); (n) LiOH·H_2O, MeOH (76%); (o) TBDMSCl, DMAP, Et_3N (100%); (p) CF_3SO_3Me, 2,6-di-*tert*-butyl-4-methylpyridine, 70 °C (66%).

to yield alcohol **22**, which was subjected to Jones oxidation followed by a Curtius rearrangement reaction[19] in the presence of 2-(trimethylsilyl)ethanol to furnish carbamate **23**. The stereochemistry of **21** and **23** was established by the NOE experiments as shown in Figure 4. Finally, to

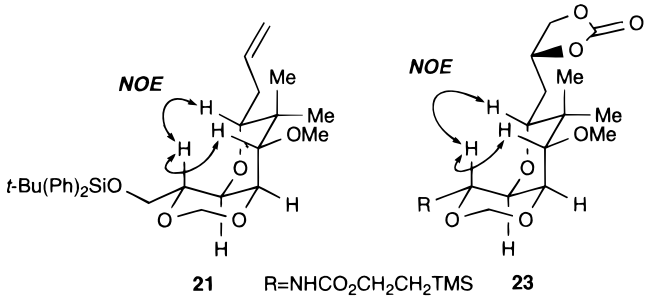


Figure 4.

confirm the structure of **23** by direct comparison, cyclic carbonate **23** was transformed into compound **3**[7c] in three steps.

In conclusion, a stereoselective synthesis of the right half of the mycalamides has been demonstrated by employing Lewis acid promoted intermolecular aldol reaction and oxypalladation as the key steps. This route would be adaptable to the preparation of onnamides and theopederins.

Acknowledgment. We thank Professor P. J. Kocienski for providing us with the spectral data of compound **3**.

OL000072V

(19) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc*. **1972**, *94*, 6203.