ORGANIC
LETTERS

2009
Vol. 11, No. 8
1809−1812

Formal Total Synthesis of *N*-Methylmaysenine

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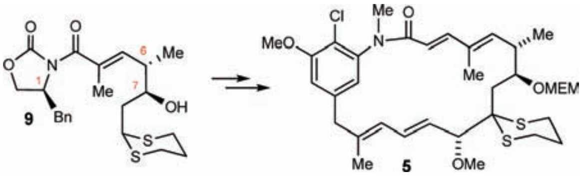
Received February 23, 2009

ABSTRACT



A novel synthetic approach for the formal total synthesis of *N*-methylmaysenine (1) has been developed. Key steps involve the Ti-mediated vinylogous Mukaiyama aldol reaction of chiral ketene silyl *N,O*-acetal with β-dithiane-substituted aldehyde, an aldol condensation, and a ring-closing metathesis reaction.

Maytansinoids are 19-membered macrolides (such as **1**−**3** in Fugure 1), and some are potent antimitotic agents, which exert exceptional cytotoxicity by disrupting microtubule assembly.[1] The antitumor activity of maytansine has been extensively evaluated in human clinical trials, but its clinical advancement was hampered by its poor therapeutic index in vivo.[2] Because of maytansinoids' distinguished biological activity, there have been numerous efforts to devise efficient syntheses of this type of natural product, culminating in total syntheses by several laboratories.[3] Recently, a novel type of ansamitocinoside P-2 (**4** in Figure 1) has been isolated from *Actinosynnema pretiosum* spp. as a potent antitumor agent by Shen and co-workers.[4] A striking feature of **4** is that its ring is decorated with an *N*-glycosyl amide side chain, rather than the *N*-methyl amide found previously in most of the maytansinoids.

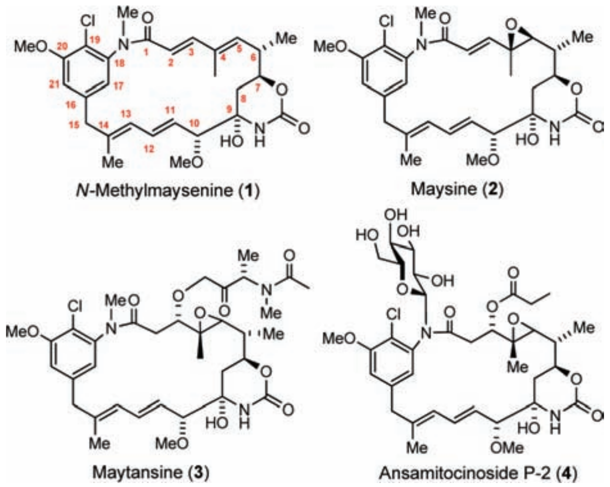


Figure 1. Biologically active maytansinoids.

Stimulated by our interest in the unusual biological properties of these structurally intriguing architectures and their natural scarcity, we have initiated a synthetic program

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(1) (a) Kupchan, S. M.; Branfman, A. R.; Sneden, A. T.; Verma, A. K.; Dailey, R. G., Jr.; Komoda, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5294. (b) Sneden, A. T; Beemsterboer, G. L. *J. Nat. Prod.* **1982**, *45*, 624. (c) Remillard, S.; Rebhum, L. I.; Howie, G. A.; Kupchan, S. M. *Science* **1975**, *189*, 1002. (d) Huang, A. B.; Lin, C. M.; Hamel, E. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 1239.

(2) Issell, B. F.; Crooke, S. T. *Cancer Treat. Rev.* **1978**, *5*, 199.

10.1021/ol900384u CCC: $40.75

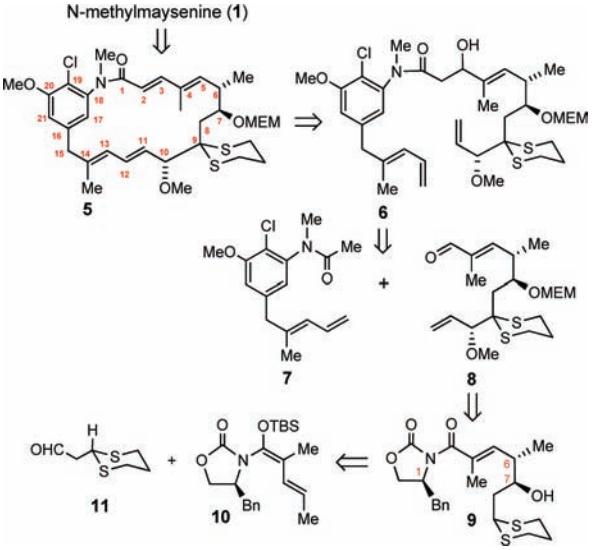
exploring efficient strategies toward these natural products themselves, as well as their structurally related analogs, which we hope could potentially lead to improve therapeutic profiles. In this paper we wish to describe the formal total synthesis of *N*-methylmaysenine (**1**), and we choose **5** as the specific synthetic target because it could act as a pivotal parent structure allowing access to all other maytansinoids.

The scaffold of maytansinoids features a conjugated diene, an *N*-substituted amide side chain, a 3-hydroxyl-[1,3]oxazinan-2-one moiety, and several stereocenters that are commonly found in polyketides. Proven strategies to reach the final macrolactam are based on amide bond formation by macrolactamazation.[3] However, this method could not apply to the newly identified maytansinoids, such as **4**, with hindered substituents on the nitrogen.

In our previous communication, we reported our progress on constructing the macrolides via diene-ene based ring-closing metathesis (RCM),[5] and this strategy was later applied successfully by Kirschning and co-workers to synthesize dechloroansamitocin $P\bar{3}$.[6]

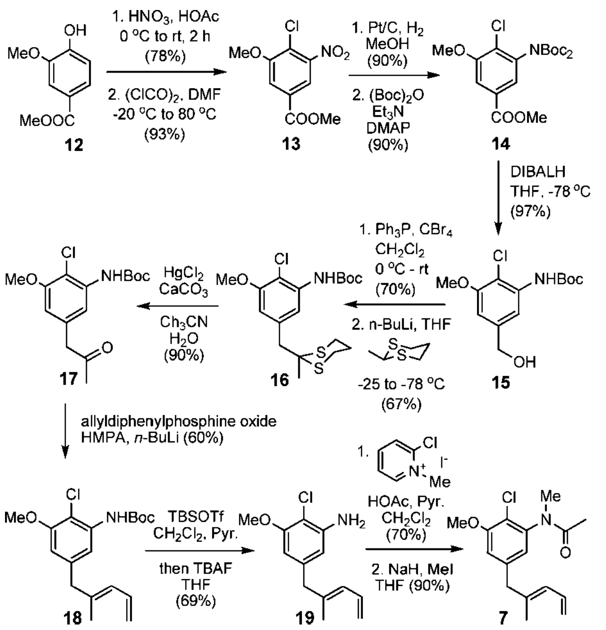
We then devised a strategy for the synthesis of **1** via the Ti-mediated vinylogous Mukaiyama aldol reaction of chiral ketene silyl *N*,*O*-acetal with β-dithiane-substituted aldehyde, an aldol condensation, and a RCM reaction as key steps (Scheme 1).

Scheme 1. Retrosynthetic Analysis



Accordingly, compound **1** was expected to be made via Corey's method from **5**,[3c] which was expected to be derived from **6** via RCM.[5,6] Fragment **6** could be made from intermediates **7** and **8** via aldol condensation, and **8** in turn could be made from **9** via a sequential formylation, vinylation, and methylation.[3i] We also envisaged that the key intermediate **9** might be prepared from **10** and **11** by using a modified Kobayashi's vinylogous Mukaiyama aldol reaction.[7]

Scheme 2. Synthesis of Fragment **7**



Our synthesis of fragment **7** therefore began with modification of Mayer's approach to make diene **18**.[8] To this end, methyl vanillate **12** first underwent nitration, followed by chlorination to afford **13** in 73% yield for two steps. Compound **13** was then subjected to hydrogenation to convert its nitro group into an amine, followed by its protection to give **14** in 81% overall yield. When **14** was next treated with DIBAL-H, its ester group was reduced to its corresponding primary alcohol accompanied by selective removal of one Boc from substrate **14** to give **15** in 97% yield. Alcohol **15** first underwent Appel reaction[9] to afford its bromide, followed by reaction with methyl dithiane anion to afford **16** in 47% yield for two steps. To make diene **18**, compound **17** first underwent 1,3-dithiane hydrolysis, followed by Wittig reaction to give diene **18** in 54% overall

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(3) (a) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916. (b) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732. (c) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. (d) Corey, E. J; Weigel, L. O.; Chamberlin, A. C.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613. (e) Meyers, A. I.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597. (f) Isobe, M.; Kitamura, M.; Goto, T. *J. Am. Chem. Soc.* **1982**, *104*, 4997. (g) Kitamura, Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252. (h) Kitanura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Org. Chem.* **1984**, *49*, 3517. (i) Benechie, M.; Khuong-Huu, F. *J. Org. Chem.* **1996**, *61*, 7133.

(4) Lu, C-H.; Bai, L-Q.; Shen, Y-M. *J. Antibiot.* **2004**, *57*, 348.

(5) Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J; Yang, Z. *Org. Lett.* **2006**, *8*, 1193. and related references cited therein.

(6) Meyer, A.; Brünjes, M.; Taft, F.; Frenzel, T.; Sasse, F.; Kirschning, A. *Org. Lett.* **2007**, *9*, 1489.

(7) Shirokawa, S.-I.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

(8) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

(9) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.

(10) (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. (b) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

yield. Finally, diene **18** was sequentially treated with TBSOTf and TBAF[10] to afford its primary amine **19**, which subsequently underwent acetylation[11] and methylation to afford the key intermediate **7** in 63% overall yield.

With **7** in hand, we next started to explore the synthesis of intermediate **8**. Since the conversion of **9** to **8** could be achieved easily by the known procedure,[3i] we therefore aimed to make intermediate **9**. Among those potential approaches surveyed, we found that enantioselective vinylogous aldol reactions seemed to be most efficient in providing a rapid access to our target. We envisaged that by using aldehyde with a dithane at its β-postion, such as **11**, the Ti-chelation transition state **A** should be favored, whereas the nonchelated Ti-complex **B** may be preferred when excess Lewis acid was used (Figure 2); as a result, we might switch the facial selectivity of the vinylogous Mukayama aldol reaction.[7,12]

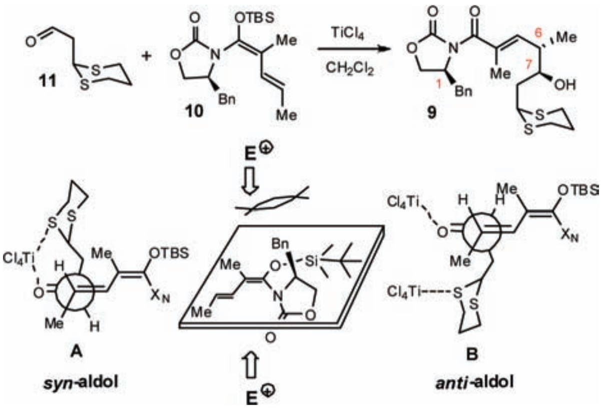
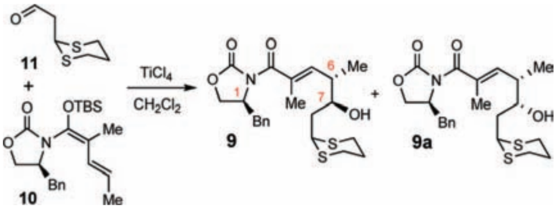


Figure 2. Rationale for vinylogous Mukaiyama aldol reaction.

To test this scenario, we prepared vinylketene silyl *N*,*O*-acetal **10** from commercially available (*E*)-2-methyl-2-pentenoic acid and (*S*)-4-benzyloxazolidin-2-one and then studied its $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction. In the event, silyl acetal **10** was reacted with aldehyde **11** to give its corresponding aldol adducts **9** and **9a** in 40% yield with 4:5 diastereoselectivity when the reaction was carried out at −65 °C in the presence of 2 equiv of $TiCl_4$. The relative as well as absolute stereochemistries for C6(*S*) and C7(*R*) in **9** was confirmed by comparasion with the compounds independently prepared through Evans' classical approach (see Supporting Information for details).

The observation of product **9** in the aldol reaction suggested that our proposed chelation complex (**A** in Figure 2) could have been formed. We therefore started to profile the conditions to imporve its diastereoselectivity. After substantial experimentation, we found that this aldol reaction could be best performed with 1.0 equiv of $TiCl_4$ at 25 °C, and products **9** and **9a** (in a ratio of 3.5/1) were obtained in 79%, albeit in moderate *syn*-selectivity (Table 1, entry 6).

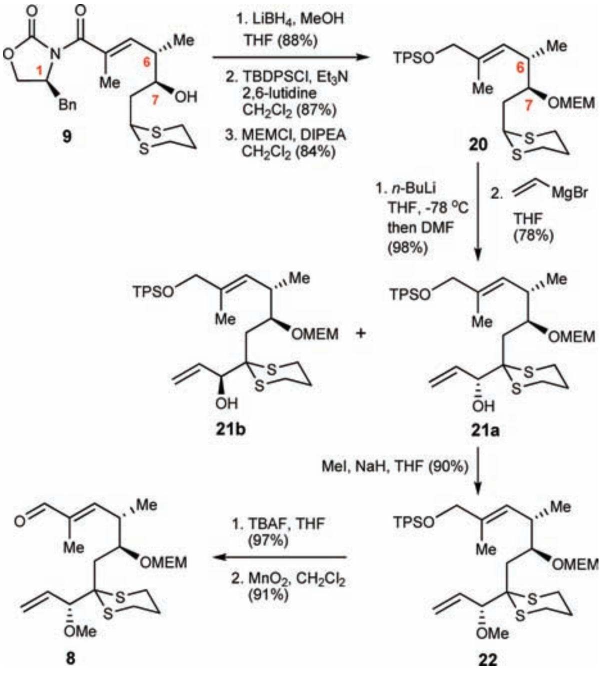
Table 1. Vinylougous Aldol Reaction between Vinylketene Silyl *N*,*O*-Acetal **10** and Aldehyde **11**



entry	temp/°C	$TiCl_4$/equiv	9:9a	yield/%
1	-65	2 equiv $TiCl_4$	4:5	40
2	-65	4 equiv $TiCl_4$	1:3	41
3	-40	1 equiv $TiCl_4$	5:3	56
4	-40	2 equiv $TiCl_4$	1:2	52
5	-10	2 equiv $TiCl_4$	5:4	73
6	rt	1 equiv $TiCl_4$	3.5:1	79

With an efficient asymmetric synthesis of fragment **9** in hand, we next set out to advance it into fragment **8**. The full sequence of reactions leading to aldehyde **8** is shown in Scheme 3. To make intermediate **20**, substrate **9** was subjected to a sequential treatment by first reaction with $LiBH_4$, followed by protection with TPS for the primary

Scheme 3. Synthesis of Fragment **8**



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(11) (a) Bald, E.; Saigo, K.; Mukayama, T. *Chem. Lett.* **1975**, 1163. (b) Bai, D. L.; Bo, Y.; Zhou, Q. *Tetrahedron Lett.* **1990**, *31*, 2161.

(12) Kobayashi and co-workers recently published in *Organic Letters* their result of a switch of facial selectivity using α-heteroatom-substituted aldehydes in the vinylogous Mukaiyama Aldol reaction, which prompts us to disclose our research. Shinoyama, M.; Shirokawa, S.-i.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277–1280.

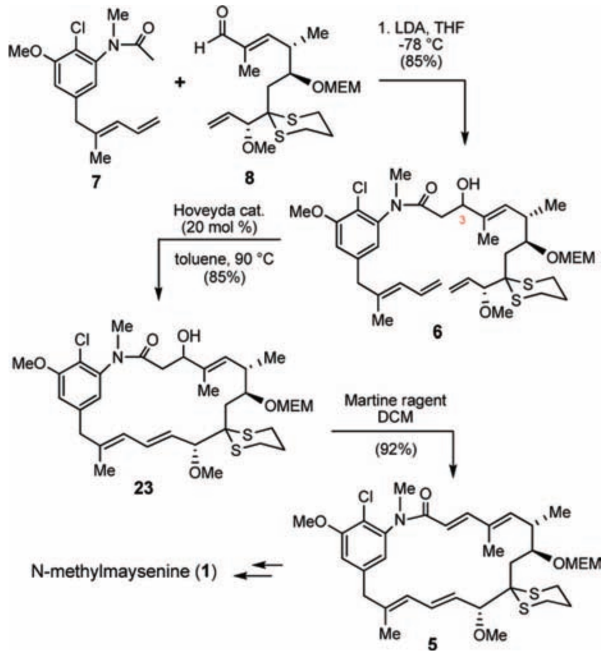
alcohol and MEM for the secondary alcohol, for 64% yield for three steps.

Compound **20** was first treated with *n*-BuLi at −78 °C followed by formylation with DMF, and the formed aldehyde was then reacted with vinyl Grinard reagent to give a pair of diastereoisomers **21a** and **21b** in 76% overall yield. The stereochemistries of **21a** and **21b** were established after **21a** was transferred to its target **5** (Scheme 4). Compound **21a** then underwent the methylation to give **22** in 90%. Thus, upon treatment with TBAF, compound **22** was converted to its free alcohol, which was then oxidized to its aldehyde **8** in 88% overall yield.

We now advanced to the stage for the completion of the formal total synthesis of *N*-methylmaysenine (**1**). To this end, amide **7** was first converted to enolide and then reacted with aldehyde **8** to give their coupling product **6** in 85% yield (Scheme 4). The subsequent RCM reaction[13] proceeded with almost complete *trans*-double bond geometry control, giving the macrolide **23** in 85% yield as a pair of diastereoisomers. Nevertheless, the diastereoisomers **23** could be converted to **5** as a single isomer by dehydration with Martine sulfurane,[14] and compound **5** was utilized as a key intermediate in the first total synthesis of *N*-methylmaysenine (**1**) by Corey and co-workers in 1980.[3d]

In summary, we have established herein an efficient route to construct the core of maytansinoids, and the developed synthetic strategy could allow us to access other maytansinoids as well. Our strategy features a switch of facial selectivities of the vinylogous Mukaiyama aldol reaction by using β-dithiane-substituted aldehyde that yielded a novel stereochemical profile matching that found in maytansinoids and other natural products.[15] To the best of our knowledge, this is the first example of direct construction of the adjacent methyl-hydroxyl *syn*-stereochemical motif by using the vinylogous Mukaiyama aldol reaction. Further studies directed toward the total synthesis of ansamitocinoside P-2 are in progress and will be reported in due course.

Scheme 4. Formal Synthesis of *N*-Methylmaysenine (**1**)



Acknowledgment. Financial support by the National Science Foundation of China (Grants 20272003, 20325208, 20832003), and the Ministry of Education of China (985 and 211 programs, and Grant 20010001027) is gratefully acknowledged. We thank Professors David Zhigang Wang, Junmin Quan, and Chuangchuang Li (The Laboratory of Chemical Genomics of Shenzhen Graduate School of Peking University) for fruitful discussion.

Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] For reviews, see: (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997. For selected examples for ring-closing metathesis, see: (d) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (e) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (f) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (g) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45. (h) Grubbs, R. H. *Adv. Synth. Catal.* **2007**, *349*, 34.

[14] (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

[15] For selected examples, see: (a) Higashide, E.; Asai, M.; Ootsu, K.; Tanida, S.; Kozai, Y.; Hasegawa, T.; Kishi, T.; Sugino, Y.; Yoneda, M. *Nature (London)* **1977**, *270*, 721. (b) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Hoto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (c) Mandala, S. M.; Thornton, R. A.; Rosenbach, M.; Milligan, J.; Garcia-Calvo, M.; Bull, H. G.; Kurtz, M. B. *J. Biol. Chem.* **1997**, *272*, 32709. (d) Nakamura, N.; Takahashi, Y.; Naganawa, H.; Nakae, K.; Imoto, M.; Shiro, M.; Matsumura, K.; Watanabe, H.; Kitahara, T. *J. Antibiot.* **2002**, *55*, 442. (e) Hong, Y.-S.; Lee, D.; Kim, W.; Jeong, J.-K.; Kim, C.-G.; Sohng, J. K.; Lee, J.-H.; Paik, S.-G.; Lee, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 11142. (f) Aldrich, C. C.; Venkatraman, L.; Sherman, D. H.; Fecik, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 8910.