Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6341–6344
Tetrahedron Letters

A practical synthesis of (−)-kazusamycin A

Shengfeng Zhou,[a] Huaxiang Chen,[a] Wensheng Liao,[a,*] Shu-Hui Chen,[a] Ge Li,[a] Ryoichi Ando[b] and Isao Kuwajima[c]

[a]*WuXi PharmaTech Co., Ltd, No. 1 Building, 288 FuTe ZhongLu, WaiGaoQiao Free Trade Zone, Shanghai 200131, PR China*
[b]*Mitsubishi Pharma Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan*
[c]*The Kitasato Institute, 1-15-1 Kitasato, Sagamihara 228-8555, Japan*

Received 19 May 2005; revised 6 July 2005; accepted 8 July 2005
Available online 25 July 2005

Abstract—We describe herein a stereo-controlled and practical synthesis of three key building blocks, namely **Segment AB′**, **Segment D**, and **Segment E′** needed for the total synthesis of (−)-kazusamycin A.

1. Introduction

Kazusamycin A, a natural product isolated from the culture broth of an actinomycete strain 81-484,[1] has demonstrated potent anti-tumor activity against a number of tumor cell lines such as P388 leukemia, Hela cells, sarcoma 180, as well as antimicrobial activity.[1,2] Kazusamycin A has also exhibited potent inhibitory activity against Rev protein translocation from the nucleus to the cytoplasm, suggesting its potential use as anti-HIV agent.[3] The absolute structure of kazusamycin A was deduced initially from NMR spectroscopic analysis, and later was confirmed by Kuwajima's first elegant total synthesis.[4] Prompted by the promising biological activity, structural complexity exhibited by kazusamycin A, and its limited availability from natural source, we became interested in designing a practical synthetic route for this natural product.[5]

In this letter, we describe the large-scale preparation of three key building blocks, namely **Segment AB′**, **Segment D**, and **Segment E′**. According to the retrosynthetic analysis outlined in Scheme 1, the availability of these intermediates should make gram-scale preparation of kazusamycin A and subsequent extensive biological and toxicological evaluation of this complex molecule possible.

2. Synthesis of Segment A (building block needed for AB′)

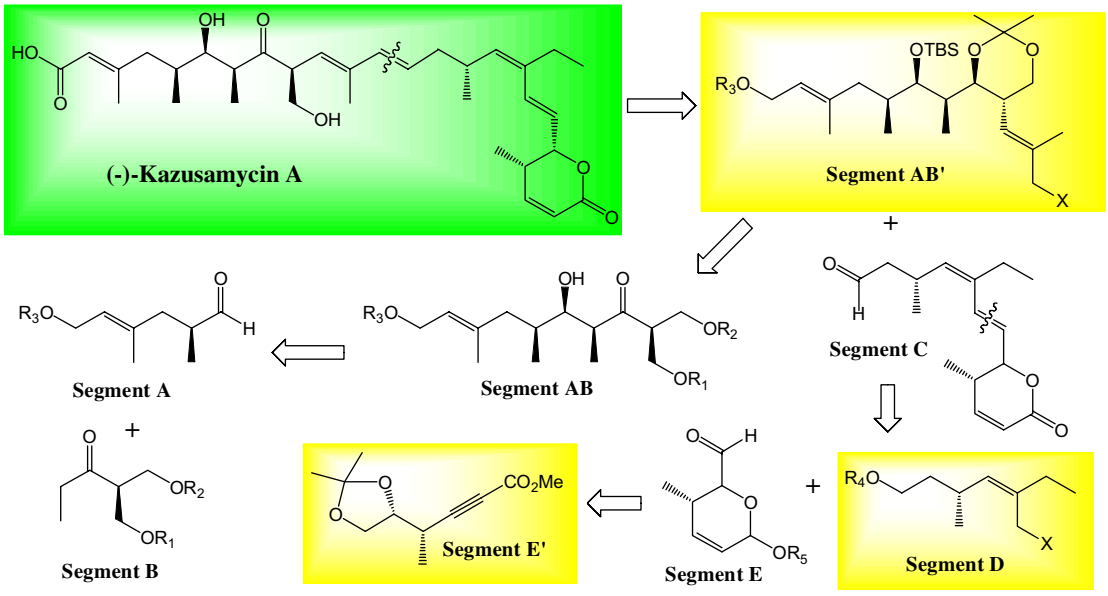
The preparation of **Segment A** was begun with *O*-benzylation of inexpensive geraniol. The resulting product **2** was subjected to epoxidation with MCPBA to give **3**, which was transformed into the acid intermediate **5** via HIO_4 mediated epoxide opening followed by the subsequent diol cleavage[6] and further oxidation with Jones reagent in an overall yield of 62% from **1**. Compound **5**[7] was converted to amide **7** via its mix-anhydride intermediate in 81% yield. Evan's chiral auxiliary induced asymmetric methylation on **7** yielded **8** (72%), which was converted to **Segment A** via $LiBH_4$ mediated amide reduction and final Swern oxidation of the resulting alcohol **9**[4] with an overall yield of 91%. Compared with Kuwajima's initial route for **Segment A**, the newly devised synthetic sequence is more economical (using geraniol as the starting material), safer (avoiding the use of dangerous free radical reaction on large scale), and more amenable for scale-up (75 g of **Segment A** made) (Scheme 2).

3. Synthesis of Segment B (building block needed for AB′)[8]

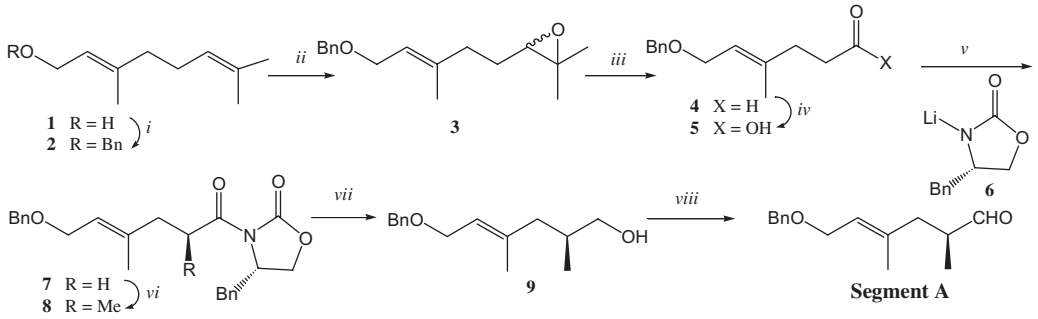
As shown in Scheme 3, saturation of enol ether **10** with ethanol led to acetal ester **11**, which was reduced with LAH to give diol **12**, thereafter the bis-benzylether **13** with 58% overall yield from **10**. Treatment of acetal **13** with TFA afforded aldehyde **14**, which was reacted with ethyl Grignard reagent to provide the desired adduct **15**

* Corresponding author. Tel.: +86 21 50461111; fax: +86 21 50463718; e-mail: liao_wensheng@pharmatechs.com

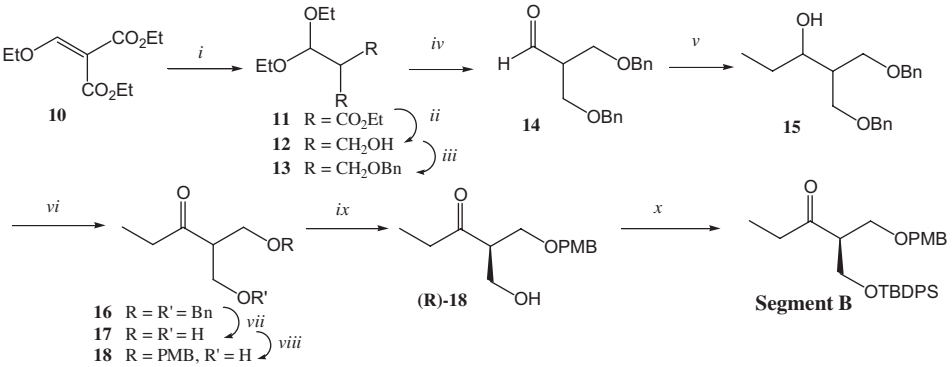
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.029



Scheme 1. Retrosynthetic analysis for kazusamycin A.



Scheme 2. Synthesis of **Segment A**: (i) NaH, BnBr; (ii) MCPBA; (iii) HIO_4; (iv) Jones oxidation, 62% (four steps); (v) *t*-BuC(O)Cl, **6**, 81%; (vi) NaHMDS, MeI, 72%; (vii) $LiBH_4$, 91%; (viii) Swern oxidation, 92%.



Scheme 3. Synthesis of **Segment B**: (i) cat. EtONa, EtOH; (ii) LAH; (iii) NaH, BnBr, 58% (three steps); (iv) TFA; (v) EtMgBr, 60–80% (two steps); (vi) Jones oxidation, 69%; (vii) Pd/C, H_2, (viii) CSA, $Cl_3CC{=}NH(OPMB)$, 71% (two steps); (ix) Lipase AK, vinyl acetate, 22%; (x) TBDPSCl, imidazole, DMF, 95%.

in 80% overall yield from **13**. Jones reagent mediated oxidation of **15** led to the keto-derivative **16** (69%), which was then subjected to de-benzylation and subsequent mono-PMB protection to give the mono alcohol **18** (71% from **16**). Treatment of **18** with lipase AK afforded chiral alcohol **(R)-18** (22%),[8] which was further converted to its silyl ester **Segment B** (95%). It is worthwhile to mention that we streamlined the synthetic

operation by performing the first three-step in a continuous fashion. In order to be cost efficient, we replaced Dess–Martin periodinane used by Kuwajima and co-workers[8] with inexpensive Jones reagent (from **15** to **16**) and carried out this sequence at 1 kg scale.

4. Synthesis of Segment AB′[4]

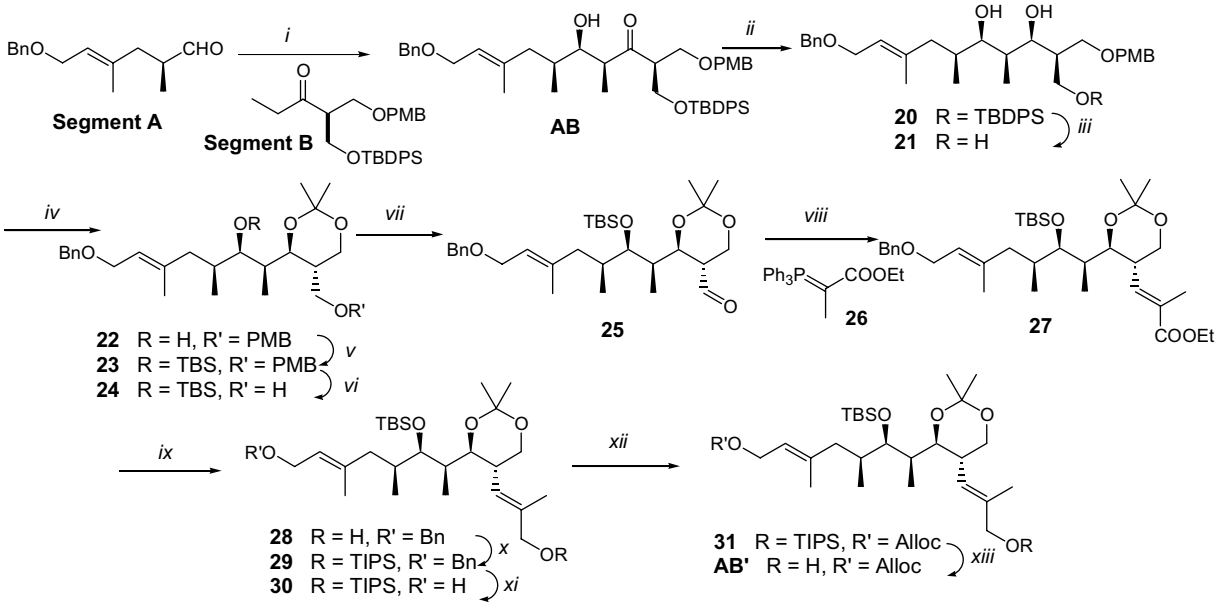
Condensation between **Segment A** and **Segment B** was promoted by $Sn(OTf)_2$ and afforded the adduct **AB** (80%) in a stereoselective fashion. The keto moiety in **Segment AB** was reduced selectively by $NaBH_4/Et_2$-BOMe to provide the syn-diol **20**, which was further desilylated to give the triol **21**. Acetonide protection of **21** yielded the mono-alcohol **22**, which was further transformed into its TBS ether **23**. The overall yield was 60% (from **Segment AB** to **23**). It should be pointed out that we conducted this four-step sequence at 100 g scale in a continuous fashion without purifying the intermediates involved. The PMB moiety in **23** was then removed by DDQ, and the resulting hydroxy group in **24** (65%) was oxidized under Swern conditions (instead of expensive Dess–Martin periodinane used previously)[4] to provide the corresponding aldehyde **25**. Reaction of **25** with the Wittig reagent **26** gave the unsaturated ester **27** (80% from **24**). Compound **27** was subjected to DIBAL-H reduction to obtain alcohol **28** (94%), thereafter the bis-silylated derivative **29** (95%). Removal of the benzyl moiety was accomplished via sodium in liquid ammonia and provided allylic alcohol **30** in variable yields. This intermediate was further converted to **Segment AB′** via *O*-acylation and followed by subsequent *O*-desilylation with an overall yield of 90% (Scheme 4).

5. Synthesis of Segment D

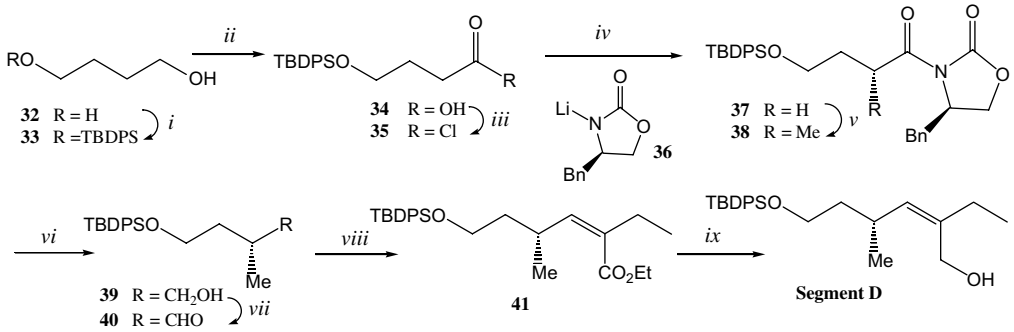
PharmaTech's approach toward the preparation of **Segment D** began with mono-silylation of 1,4-butanediol **32** to obtain mono-alcohol **33** (87%), which was oxidized with PDC to provide acid **34** (61%), followed by treatment with ClC(O)C(O)Cl to give acid chloride **35**.[9] Reaction of **35** with the lithiated Evans chiral auxiliary **36** provided the desired adduct **37** in an overall yield of 72% from **34**. Asymmetric *C*-methylation on **37** yielded **38** with high level of diastereoselectivity. Compound **38** was converted to alcohol **39**[10] and then aldehyde **40**[11] via $LiBH_4$ reduction and subsequent Swern oxidation. This aldehyde was subjected to Ando's *cis*-olefination[12] to afford **41**[13] (78% for two steps), which was treated with DIBAL-H to produce the desired **Segment D** in 92% yield. Compared with the literature route for **Segment D**, the synthetic route employed at PharmaTech was more amenable for scale-up due to relatively short sequence and readily available starting material. Furthermore, the more expensive Dess–Martin reagent was replaced by Swern oxidation with similar yield (Scheme 5).

6. Synthesis of Segment E′

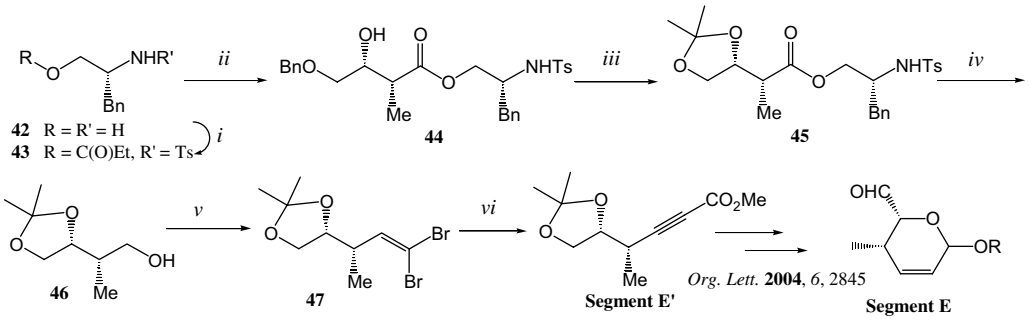
As highlighted in Scheme 6, *N*- and *O*-acylation of amino alcohol **42** yielded **43** in excellent yield. The following titanium enolate mediated aldol condensation between **43** and $BnOCH_2CHO$ provided the *syn*-adduct **44**[14] with high enantioselectivity. The synthetic approach used herein for establishing absolute stereochemistry (two newly formed chiral centers) was different from that used by Kuwajima and co-workers.[4] In that case, the Evans chiral auxiliary was employed as the



Scheme 4. Synthesis of **Segment AB′**: (i) $Sn(OTf)_2$, triethylamine, 80%; (ii) Et_2BOMe, $NaBH_4$; (iii) TBAF, THF; (iv) $Me_2C(OMe)_2$, PPTS; (v) TBSOTf, 2,6-lutidine, 60% (four steps); (vi) DDQ, 65%; (vii) Swern; (viii) **26**, toluene, 80% (two steps); (ix) DIBAL-H, 94%; (x) TIPSCl, imidazole, DMF, 95%; (xi) Na/NH_3, 33–80%; (xii) AllocCl, pyridine; (xiii) TBAF, 90% (two steps).



Scheme 5. Synthesis of **Segment D**: (i) n-BuLi, TBDPSCl, 87%; (ii) PDC, DMF, 61%; (iii) $(COCl)_2$; (iv) **36**, 72% (two steps); (v) NaHMDS, MeI, 74%; (vi) $LiBH_4$, 95%; (vii) Swern; (viii) $(o\text{-MeOPhO})_2P(O)CH(Et)CO_2Et$, NaH, 78% (two steps); (ix) DIBAL-H, 92%.



Scheme 6. Synthesis of **Segment E′**: (i) TsCl, Et_3N, then $EtC(O)Cl$, Et_3N, >90%; (ii) $TiCl_4$, DIEA, $BnOCH_2CHO$; (iii) H_2, Pd/C, then $Me_2C(OMe)_2$; (iv) LAH, 80% (four steps); (v) Swern, then CBr_4, PPh_3, 50% (two steps); (vi) *n*-BuLi, $ClCO_2Me$, 81%.

chirality-inducing source. With compound **44** in hand, the *O*-Bn moiety of which was removed by standard hydrogenation, and the resulting diol was subjected to acetonide protection to yield **45**. LAH mediated ester reduction on **45** provided alcohol **46**[15] in 80% overall yield (four steps from **43**). Alcohol **46** was oxidized under Swern conditions to provide its corresponding aldehyde intermediate, which was further treated with triphenylphospine and carbon tetrabromide to afford the α,α-dibromo-olefin **47** in 50% overall yield. Final treatment of **47** with *n*-BuLi and chloromethylformate thus provided the desired alkyne derivative **Segment E′**. It should be pointed out that further conversion of **Segment E′** to **Segment E** was reported by Kuwajima and co-workers.[4]

In summary, we have accomplished practical, large-scale preparations of **Segment AB′**, **Segment D**, and **Segment E′**, needed for total synthesis of kazusamycin A. All of the three building blocks were prepared via newly designed synthetic sequences with the intention to avoid using expensive starting materials, hazardous reagents, and labor-intensive chromatographic separation.

Acknowledgements

We thank Mr. Jianyi Ma, Chonggang Liu, Shengbin Li, and Xia Li for their help with synthetic work. We are also indebted to the chemists from Analytic Department at WuXi PharmaTech for their support.

References and notes

1. Umezawa, I.; Komiyama, K.; Oka, H.; Okada, K.; Tomisaka, S.; Miyano, T.; Takano, S. *J. Antibiot.* **1984**, *37*, 706–711.
2. Komiyama, K.; Okada, K.; Hirokawa, Y.; Masuda, K.; Tomisaka, S.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 224–229.
3. Wang, Y.; Ponelle, M.; Sanglier, J.-J.; Wolff, B. *Helv. Chim. Acta* **1997**, *80*, 2157–2167.
4. Arai, N.; Chikaraishi, N.; Omura, S.; Kuwajima, I. *Org. Lett.* **2004**, *6*, 2845–2848.
5. Zhou, S-F.; Chen, H-X.; Liao, W.; Chen, S. H.; Li, G.; Ando, R.; Kuwajima, I. Presented at the Poster Section in Organic Chemistry Division, 13–18 March 2005, San Diego, CA. Abst.#ORGN-576.
6. Chen, K.-M.; Semple, J. E.; Joullie, M. M. *J. Org. Chem.* **1985**, *50*, 3997–4005.
7. Ple, P. A.; Hamon, A.; Jones, G. *Tetrahedron* **1997**, *53*, 3395–3400.
8. Arai, N.; Chikaraishi, N.; Ikawa, M.; Omura, S.; Kuwajima, I. *Tetrahedron: Asymmetry* **2004**, *15*, 733–741.
9. Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306–313.
10. Aiguade, J.; Hao, J.-L.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817–820.
11. Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993–2012.
12. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.
13. Vicario, J. L.; Job, A.; Wolberg, M.; Muller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023–1026.
14. Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2002**, *43*, 5621–5624.
15. Ojika, M.; Kigoshi, H.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8505–8508.