Communications

Natural Products

DOI: 10.1002/anie.200602860

Total Synthesis of IKD-8344**

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IKD-8344 (1, Scheme 1) is a novel 28-membered ring macrodiolide antibiotic from an unidentified alkalophilic Actinomycete, strain no. 8344,^[1] which exhibits potent anthelmintic activity against *Trichinella spiralis* and strong cytotoxicity against L5178Y mouse leukemia cells with an IC₅₀ value of 0.54 ngmL^{-1,[1]} More recently, it was also isolated from *Streptomyces* sp. A6792 and selective antifungal activities against the mycelial form of *Candida albicans* were noted.^[2]

The unique bioactivities and stereochemical complexities of the molecule make it an attractive synthetic target. The monomeric *seco* acid **A** (Scheme 1) contains three methyl branches and three oxolane units: a *threo* (C2–C3)–*trans* (C3– C6) array is connected to a *threo* (C9–C10)–*cis* (C10–C13) arrangement, which is flanked by another *threo* (C16–C17)– *trans* (C17–C20) unit. Efficient and stereoselective construction and assemblage of these structural units is not trivial, and

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^[**] This work was supported by a grant from the Center for Bioactive Molecular Hybrids (Yonsei University and KOSEF), and a grant from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea. BK21 graduate fellowship grants to W.H.K., S.K.H., S.M.L., S.K.J., and Y.W.K. are gratefully acknowledged.



Scheme 1. Retrosynthetic analysis.

the difficulty therein is manifested by the absence of reports on the total synthesis of IKD-8344 (1) in the literature.^[3] In the retrosynthetic analysis, synthesis of 1 would be accomplished through dimerization of the monomeric *seco* acid **A**, which may be prepared by coupling of fragments **B** and **D**. Fragment **B** may be obtained by radical cyclization of the β alkoxymethacrylate derivative **C**, which should be accessible from fragment **D**. A reliable synthesis of fragment **D** is prerequisite for a successful total synthesis of this intriguing molecule, which is described in this communication.

Synthesis of the B fragment commenced with the aldol reaction of aldehyde $3^{[4]}$ with the boron enolate of the chiral imide 2 (Scheme 2).^[5] Reduction of the product aldol imide and silvl protection of the primary hydroxy group afforded alcohol 4. The threo-trans oxolane derivative 5 was obtained by mesylation of 4, acetonide deprotection, and treatment with base. The corresponding mesylate 6 was converted into aldehyde 7 by silvl deprotection and PCC oxidation. Reaction of 7 with allyltrimethylsilane in the presence of titanium chloride led to a 4:1 mixture,^[6] favoring **8**, of the homoallylic alcohols. At this point, the mesyloxy group was removed through LiAlH₄ reduction, and the aldehyde obtained by ozonolysis after benzyl protection was converted stereoselectively into the homoallylic alcohol 9 by reaction with allyltributylstannane in the presence of magnesium bromide etherate.^[7] Iodide **11** was obtained from **9** by ozonolysis, sodium borohydride reduction, tosylation of the primary hydroxy group, reaction with the dimethyl acetal 10,^[8] and iodide substitution. Radical cyclization^[9] of β-alkoxymethacrylate 11 proceeded smoothly to produce selectively (10:1) the threo-cis oxolane product 12 in good yield (Scheme 2).^[10]

Coupling of fragments **B** and **D** was problematic. For example, the dithiane derivative prepared from ester 12 was not amenable to the reaction with mesylate **6**. After considerable exploration, it was found that efficient coupling was possible by employing a Wittig reaction. Aldehyde 13 was



Scheme 2. Preparation of the **B** fragment. a) **2**, Bu₂BOTf, NEt₃, CH₂Cl₂, $-40 \rightarrow 0^{\circ}$ C; **3**, -78° C; b) LiBH₄, diethyl ether, 0° C \rightarrow RT; c) TBDPSCl, imidazole, CH₂Cl₂; d) MsCl, NEt₃, CH₂Cl₂, 0° C \rightarrow RT; e) CSA, MeOH; f) NaHMDS, THF, 0° C \rightarrow RT; g) MsCl, NEt₃, CH₂Cl₂, 0° C \rightarrow RT; h) TBAF, THF; i) PCC, 4-Å MS, CH₂Cl₂; j) CH₂CHCH₂SiMe₃, TiCl₄, CH₂Cl₂, -78° C; k) LiAlH₄, diethyl ether, 0° C \rightarrow RT; l) NaHMDS, BnBr, THF/DMF (5:1), 0° C \rightarrow RT; m) O₃, CH₂Cl₂, -78° C; Ph₃P; n) CH₂CHCH₂SnBu₃, MgBr₂·Et₂O, CH₂Cl₂; o) O₃, CH₂Cl₂, -78° C; Ph₃P; p) NaBH₄, MeOH, 0° C \rightarrow RT; q) TsCl, NEt₃, CH₂Cl₂, 0° C; r) **10**, PPTS, benzene, reflux; s) Nal, acetone, reflux; t) Bu₃SnH, Et₃B, toluene, air, -78° C. Tf = trifluoromethanesulfonyl, TBDPS = *tert*-butyldiphenylsilyl, Ms = methanesulfonyl, CSA = (±)-camphorsulfonic acid, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TBAF = tetrabutylammonium fluoride, PCC = pyridinium chlorochromate, Bn = benzyl, Ts = toluene-4-sulfonyl, PPTS = pyridinium *p*-toluenesulfonate.

prepared from the primary alcohol 5 (Scheme 3). Ester 12 was converted into the corresponding phosphonium salt by lithium borohydride reduction, iodide substitution, and reaction with triphenylphosphine, and the ylide obtained from the phosphonium salt reacted with aldehyde 13 to produce olefin 14 in good yield. A mixture of epoxides was obtained from 14 by oxidation with mCPBA. Reaction of the mixture with excess lithium aluminum hydride, Dess-Martin oxidation of the diol produced, and chlorite oxidation of the aldehyde functionality provided regioselectively (12:1) the correct keto carboxylic acid 15. Use of diisobutylaluminum hydride (DIBAH) as the reducing agent eventually produced the alternative ketone as the major product. The monomeric seco acid 16 was prepared by hydrogenolysis. The secondary alcohol 17 was obtained from 15 by TBDPS protection and hydrogenolysis (Scheme 3).

Direct macrodiolide formation of the monomeric seco acid 16 did not proceed. A relatively low yield of the

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Scheme 3. Preparation of the A fragment. a) $SO_3 \cdot pyridine$, NEt_3 , $DMSO/CH_2Cl_2$ (1:1); b) $LiBH_4$, diethyl ether, $0^{\circ}C \rightarrow RT$; c) l_2 , Ph_3P , imidazole, THF, $0^{\circ}C \rightarrow RT$; d) Ph_3P , MeCN, reflux; e) BuLi, THF, $-78^{\circ}C$; 13; f) mCPBA, CH_2Cl_2 , $0^{\circ}C$; g) $LiAlH_4$, diethyl ether, $0^{\circ}C$; h) Dess-Martin periodinane (3.0 equiv), CH_2Cl_2 ; i) $NaClO_2$ (1.3 equiv), NaH_2PO_4 (1.3 equiv), tBuOH/2-methyl-2-butene/ H_2O (10:5:1); j) H_2 , Pd/C, MeOH; k) TBDPSCl (4.0 equiv), imidazole (7.0 equiv), DMAP(0.5 equiv), CH_2Cl_2 ; l) H_2 , $Pd(OH)_2/C$, EtOAc. mCPBA = 3-chloroperoxybenzoic acid, DMAP = 4-dimethylaminopyridine.

macrolide product **18** was obtained under a variety of conditions (Scheme 4).^[11] The coupling reaction of **15** and **17**, however, proceeded efficiently under standard Yamaguchi



Scheme 4. Cyclization of the *seco* acid. a) CDIC (2.5 equiv), Cs_2CO_3 (1.0 equiv), CH_2Cl_2 (0.02 M), 0°C; DMAP (20 equiv). CDIC = 2-chloro-1,3-dimethylimidazolinium chloride, s.m. = recovered starting material.

conditions to afford ester **19** (Scheme 5). The dimeric *seco* acid **20** was obtained efficiently through TBDPS deprotection and hydrogenolysis. IKD-8344 (1)^[12] was finally obtained upon lactonization of **20** under modified Yamaguchi conditions (Scheme 5).^[13]

The present synthesis is another example of the application of β -alkoxymethacrylate radical cyclization reactions^[9] for the stereoselective construction of complex oxacyclic natural products.



Scheme 5. Synthesis of IKD-8344. a) **15** (1.0 equiv), 2,4,6-Cl₃PhCOCl (1.7 equiv), NEt₃ (3.5 equiv), THF (0.025 м); **17** (1.3 equiv), DMAP (3.0 equiv), benzene (0.02 м); b) conc. HCl, MeOH; c) H₂, Pd(OH)₂/C, EtOAc; d) 2,4,6-Cl₃PhCOCl (40 equiv); NEt₃ (60 equiv), DMAP (20 equiv), toluene (0.15 μm), reflux.

Experimental Section

Ester 12: nBu₃SnH (0.018 mL, 0.07 mmol) and Et₃B (1.0M in hexane, 0.088 mL) were added to a solution of iodide 11 (31 mg, 0.058 mmol) in toluene (6 mL) at -78 °C. The resulting solution was stirred for 1 h under air at -78 °C. Concentration and purification of the residue by flash column chromatography (hexanes/EtOAc, 4:1) furnished ester 12 (21.5 mg, 91%): $R_{\rm f} = 0.31$ (hexanes/EtOAc, 4:1); ¹H NMR (300 MHz, CDCl₃): $\delta = 7.33-7.24$ (m, 5H), 4.53 and 4.47 (AB q, 2H, J_{AB}=11.3 Hz), 4.08-3.99 (m, 3H), 3.86-3.78 (m, 2H), 3.69 (s, 3H), 2.60-2.55 (m, 1H), 2.05-1.90 (m, 6H), 1.70-1.39 (m, 5H), 1.19 (d, 3H, J = 6.0 Hz), 1.11 (d, 3H, J = 7.0 Hz), 0.82 ppm (d, 3H, J =6.9 Hz); ¹³C NMR (75 MHz, CDCl₃): $\delta = 175.5$, 139.2, 128.2, 127.7, 127.2, 80.0, 79.6, 77.9, 77.2, 74.6, 71.6, 51.6, 45.2, 40.6, 36.5, 33.9, 31.6, 30.7, 28.4, 21.4, 13.1, 10.0 ppm; IR (neat): $v_{max} = 3029$, 2967, 2877, 1739, 1455, 1376, 1197, 1068, 736, 698 cm⁻¹; MS (CI): m/z (relative intensity): 405 [M⁺+1] (81), 297 (100), 295 (28), 279 (11), 213 (63), 183 (31), 157 (42), 91 (23); HRMS (CI): calcd for $C_{24}H_{37}O_5 [M^+ + 1]$: 405.2641; found: 405.2641; $[\alpha]_{D}^{27} = +14.0$ (*c* = 1.16, CHCl₃).

IKD-8344 (1): The dimeric seco acid 20 (15 mg, 0.017 mmol) was dissolved in toluene (113 mL). NEt₃ (0.15 mL, 1.04 mmol), 2,4,6trichlorobenzoyl chloride (0.11 mL, 0.70 mmol), and DMAP (42 mg, 0.35 mmol) were added at room temperature, and then the solution was heated under reflux for 4 h. The reaction was quenched by addition of saturated NH₄Cl solution (100 mL) and the reaction mixture was extracted with CH_2Cl_2 (150 mL \times 3). The organic extracts were dried over MgSO₄, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/EtOAc, 2:1) gave IKD-8344 (1, 9.5 mg, 65%): $R_f = 0.28$ (hexanes/EtOAc, 2:1); ¹H NMR (300 MHz, CDCl₃): $\delta = 5.32-5.28$ (m, 2H), 4.38–4.31 (m, 2H), 4.15-4.01 (m, 4H), 3.96-3.87 (m, 4H), 3.82-3.76 (m, 2H), 2.95-2.83 (m, 4H), 2.46-2.26 (m, 6H), 2.19-2.13 (m, 2H), 2.03-1.90 (m, 9H), 1.81-1.73 (m, 3H), 1.68-1.59 (m, 5H), 1.51-1.38 (m, 9H), 1.18 (d, 6H, J = 6.0 Hz), 1.09 (d, 6H, J = 7.4 Hz), 1.00 (d, 6H, J = 7.3 Hz),0.83 ppm (d, 6H, J = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃): $\delta = 212.0$, 175.1, 80.5, 80.0, 79.5, 75.2, 74.9, 74.8, 72.2, 53.4, 45.6, 45.6, 41.1, 36.2, 33.9, 32.1, 30.9, 30.7, 29.6, 29.4, 21.2, 14.4, 13.7, 10.9 ppm; MS (FAB): m/z (relative intensity): 867 $[M^+ + Na]$ (58), 883 (45), 845 (14), 423 (12), 307 (22), 289 (11), 209 (43), 154 (83), 85 (100); HRMS (FAB): calcd for C₄₈H₇₆O₁₂Na [M^+ + Na]: 867.5235; found: 867.5239; [α]¹⁵_D = $+39.7 (c = 0.25, CHCl_3).$

Received: July 18, 2006 Published online: October 2, 2006 **Keywords:** anticancer agents · antifungal agents · macrodiolides · natural products · total synthesis

- a) Y. Minami, K. Yoshida, R. Azuma, M. Nishii, J. Inagaki, F. Nohara, *Tetrahedron Lett.* **1992**, *33*, 7373–7376; b) T. Ishida, Y. In, M. Nishii, Y. Minami, *Chem. Lett.* **1994**, 1321–1322.
- [2] E. I. Hwang, B. S. Yun, W. H. Yeo, S. H. Lee, J. S. Moon, Y. K. Kim, S. J. Lim, S. U. Kim, *J. Microbiol. Biotechnol.* 2005, 15, 909–912.
- [3] For a report on the synthesis of the fragments, see: W. Jiang, D. A. Lantrip, P. L. Fuchs, Org. Lett. 2000, 2, 2181–2184.
- [4] For an example of the use of this known aldehyde, see: A. B. Smith III, D.-S. Kim, J. Org. Chem. 2006, 71, 2547–2557.
- [5] For an example of asymmetric aldol reactions, see: D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* 1990, *112*, 7001–7031.
- [6] Formation of the desired *anti-anti* product was problematic. For example, Roush allylation by using isopropyl (*S,S*)-tartrate yielded a mixture of the products favoring (1:2) the wrong isomer. For detailed discussions, see: D. A. Evans, B. D. Allison, M. G. Yang, C. E. Masse, *J. Am. Chem. Soc.* 2001, *123*, 10840– 10852.
- [7] For the use of magnesium bromide etherate in an allylstannane reaction, see: E. Lee, E. J. Jeong, E. J. Kang, L. T. Sung, S. K. Hong, J. Am. Chem. Soc. 2001, 123, 10131–10132.
- [8] R. D. Walkup, N. U. Obeyesekere, Synthesis 1987, 607-611.
- [9] For recent examples of β-alkoxyacrylate and β-alkoxymethacrylate radical cyclization, see: a) E. J. Kang, E. J. Cho, M. K. Ji, Y. E. Lee, D. M. Shin, S. Y. Choi, Y. K. Chung, J.-S. Kim, H.-J. Kim, S.-G. Lee, M. S. Lah, E. Lee, J. Org. Chem. 2005, 70, 6321 6329; b) H. Y. Song, J. M. Joo, J. W. Kang, D.-S. Kim, C.-K. Jung, H. S. Kwak, J. H. Park, E. Lee, C. Y. Hong, S. Jeong, K. Jeon, J. H. Park, J. Org. Chem. 2003, 68, 8080–8087; c) E. J. Jeong, E. J. Kang, L. T. Sung, S. K. Hong, E. Lee, J. Am. Chem. Soc. 2002, 124, 14655–14662; d) E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim, W. S. Jang, Angew. Chem. 2002, 114, 184–186; Angew. Chem. Int. Ed. 2002, 41, 176–178.
- [10] E. Lee, S. J. Choi, Org. Lett. 1999, 1, 1127-1128.
- [11] See, for example: A. Fürstner, J. Mlynarski, M. Albert, J. Am. Chem. Soc. 2002, 124, 10274-10275.
- [12] $[\alpha]_D^{15} = +39.7$ (c = 0.25, CHCl₃; literature: $[^{1a}] [\alpha]_D^{17} = +40.2$). The spectral data of the synthetic sample were identical with those of the natural product.
- [13] For the use of the modified Yamaguchi conditions, see: D. A. Evans, H. P. Ng, D. L. Rieger, J. Am. Chem. Soc. 1993, 115, 11446-11459.