Natural Products

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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 IC_{50} value of 0.54 ng mL^{-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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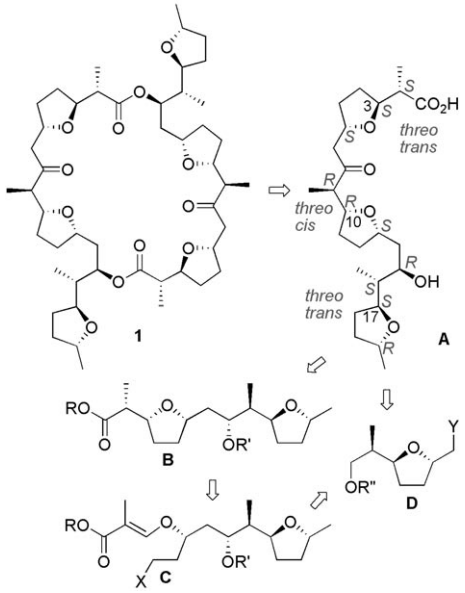
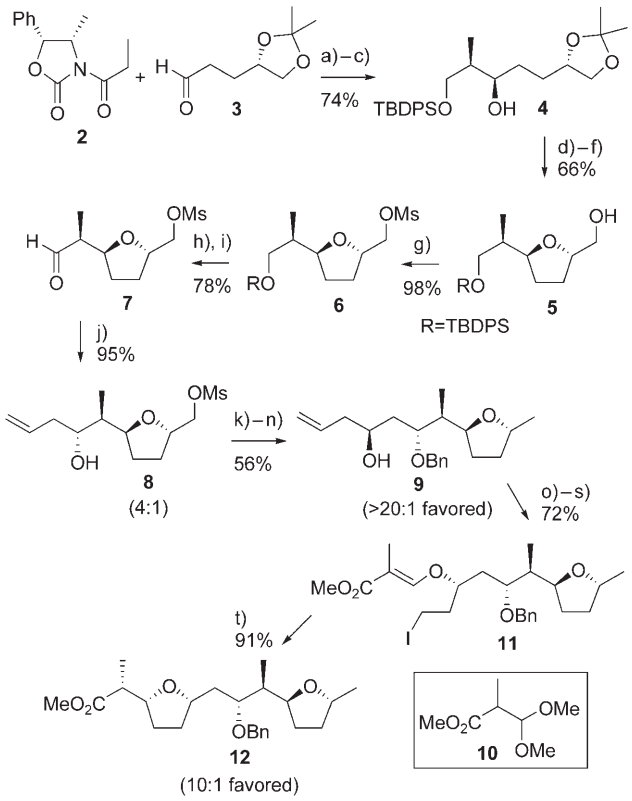
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Retrosynthetic analysis.



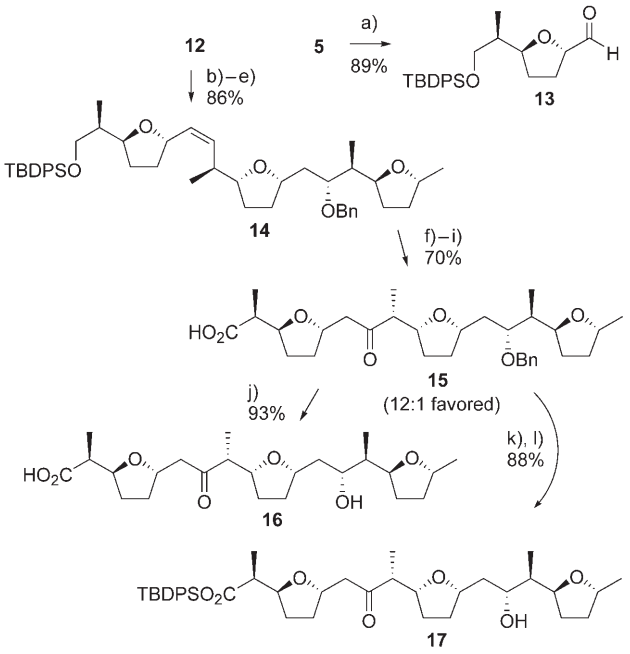
Scheme 2. Preparation of the **B** fragment. a) **2**, Bu_2BOTf, NEt_3, CH_2Cl_2, −40→0°C; **3**, −78°C; b) $LiBH_4$, diethyl ether, 0°C→RT; c) TBDPSCl, imidazole, CH_2Cl_2; d) MsCl, NEt_3, CH_2Cl_2, 0°C→RT; e) CSA, MeOH; f) NaHMDS, THF, 0°C→RT; g) MsCl, NEt_3, CH_2Cl_2, 0°C→RT; h) TBAF, THF; i) PCC, 4-Å MS, CH_2Cl_2; j) $CH_2CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −78°C; k) $LiAlH_4$, diethyl ether, 0°C→RT; l) NaHMDS, BnBr, THF/DMF (5:1), 0°C→RT; m) O_3, CH_2Cl_2, −78°C; Ph_3P; n) $CH_2CHCH_2SnBu_3$, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2; o) O_3, CH_2Cl_2, −78°C; Ph_3P; p) $NaBH_4$, MeOH, 0°C→RT; q) TsCl, NEt_3, CH_2Cl_2, 0°C; r) **10**, PPTS, benzene, reflux; s) NaI, acetone, reflux; t) Bu_3SnH, Et_3B, 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.

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 silyl 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 silyl 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 $LiAlH_4$ 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]

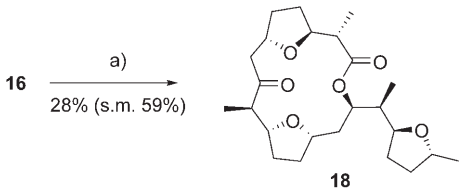
Coupling of fragments **B** and **D** was problematic. For example, the dithiane derivative prepared from ester **12** was not amenable to the reaction with mesylate **6**. After considerable exploration, it was found that efficient coupling was possible by employing a Wittig reaction. Aldehyde **13**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



Scheme 3. Preparation of the **A** fragment. a) SO_3·pyridine, NEt_3, DMSO/CH_2Cl_2 (1:1); b) $LiBH_4$, diethyl ether, 0 °C→RT; c) I_2, Ph_3P, imidazole, THF, 0 °C→RT; d) Ph_3P, MeCN, reflux; e) BuLi, THF, −78 °C; **13**; f) *m*CPBA, CH_2Cl_2, 0 °C; g) $LiAlH_4$, diethyl ether, 0 °C; h) Dess–Martin periodinane (3.0 equiv), CH_2Cl_2; i) $NaClO_2$ (1.3 equiv), NaH_2PO_4 (1.3 equiv), *t*BuOH/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. *m*CPBA = 3-chloroperoxybenzoic acid, DMAP = 4-dimethylaminopyridine.

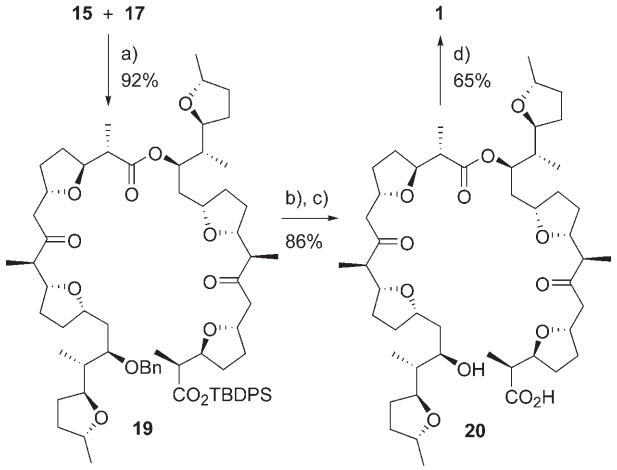
macrolide product **18** was obtained under a variety of conditions (Scheme 4).[11] The coupling reaction of **15** and **17**, however, proceeded efficiently under standard Yamaguchi



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-Cl_3PhCOCl (1.7 equiv), NEt_3 (3.5 equiv), THF (0.025 M); **17** (1.3 equiv), DMAP (3.0 equiv), benzene (0.02 M); b) conc. HCl, MeOH; c) H_2, $Pd(OH)_2$/C, EtOAc; d) 2,4,6-Cl_3PhCOCl (40 equiv); NEt_3 (60 equiv), DMAP (20 equiv), toluene (0.15 μM), reflux.

Experimental Section

Ester **12:** nBu_3SnH (0.018 mL, 0.07 mmol) and Et_3B (1.0 M 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 %): $R_f = 0.31$ (hexanes/EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$–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); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.5$, 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): $\nu_{max} = 3029$, 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; $[\alpha]_D^{27} = +14.0$ ($c = 1.16$, $CHCl_3$).

IKD-8344 (**1**): The dimeric *seco* acid **20** (15 mg, 0.017 mmol) was dissolved in toluene (113 mL). NEt_3 (0.15 mL, 1.04 mmol), 2,4,6-trichlorobenzoyl 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 NH_4Cl solution (100 mL) and the reaction mixture was extracted with CH_2Cl_2 (150 mL × 3). The organic extracts were dried over $MgSO_4$, 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); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.32$–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); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 212.0$, 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 $C_{48}H_{76}O_{12}Na$ [$M^+ + Na$]: 867.5235; found: 867.5239; $[\alpha]_D^{15} = +39.7$ ($c = 0.25$, $CHCl_3$).

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