Enantioselective Synthesis of the Tricyclic Core of GKK1032, Novel Antibiotic Anti-Tumor Agents, by Employing an Intramolecular Diels–Alder Cycloaddition Strategy

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Abstract: An efficient and enantioselective synthesis of a decahydrofluorene nucleus, the tricyclic core (ABC-ring system) of GKK1032s, novel antimicrobial and anti-tumor agents, was achieved using a highly diastereoselective intramolecular Diels–Alder (IMDA) reaction. The substrate for the IMDA reaction was synthesized through intermolecular Diels–Alder reaction of Kitahara–Danishefsky's diene and an enone derived from enulose to construct the functionalized C-ring. CuCl-promoted Stille coupling of a vinyl iodide and a vinylstannane installed the requisite triene side chain.

Key words: Diels–Alder reaction, Stille coupling, natural product synthesis, GKK1032s, antimicrobial agents, anti-tumor agents

In 2001, GKK1032A$_1$ (**1**), A$_2$ (**2**), and B (**3**) were isolated by the Kyowa Hakko research group from the culture broth of *Penicillium* sp. GKK1032 (Figure 1).[1] In addition to displaying antimicrobial activity against *Bacillus subtilis* No.10707, these compounds exhibit anti-tumor activity against the human cervical cancer-derived HeLa S3 cells. Just one year later, Ōmura et al. also reported the isolation of FO-7711CD6 from the culture broth of *Penicillium* sp., whose planar structure was incidentally identical to that of GKK1032A$_2$ (**2**).[2] Subsequently, He et al. disclosed the isolation of pyrrocidines A (**4**) and B (**5**) from the fermentation broth of a fungus, *LL*-Cyan426, and their structures were assigned as the analogues of GKK1032s.[3] These natural products have novel and quite unique structural features that include a common decahydrofluorene nucleus (ABC-ring) incorporated with an unusual 12- or 13-membered macrocycle, through ethereal and carbonyl linkages.

The gross structure and stereochemistry of GKK1032s were assigned based on exhaustive spectroscopic studies and the relative stereochemistry of **3** was determined by X-ray crystallographic analysis, while their absolute configurations have not been revealed.

The interesting biological properties and unique structural features, as well as the unknown absolute stereochemistry, prompted us to undertake a project directed toward the

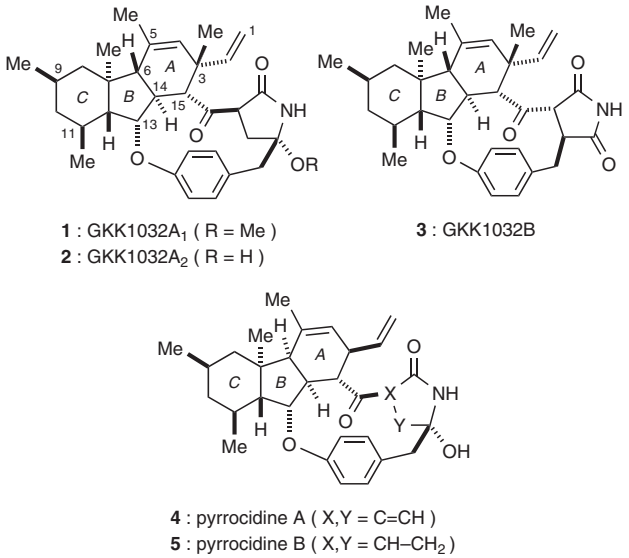

Figure 1 Structures of GKK1032A$_1$ (1), A$_2$ (**2**), B (**3**) and pyrrocidines A (**4**), B (**5**).

total synthesis of GKK1032s (**1**–**3**) in enantiomerically pure form. A possible biosynthetic pathway to GKK1032A$_2$ (**2**) was recently reported by Oikawa;[4] however, to the best of our knowledge, synthetic studies of GKK1032s and pyrrocidines have not appeared in the literature to date. Herein, we report our preliminary results concerning an efficient and enantioselective synthesis of decahydrofluorene nucleus **6**, which represents the first entry to the tricyclic core (ABC-ring) of GKK1032s.[5]

Our synthetic plan for the target molecule **6** is outlined in Scheme 1. The most crucial step in this scheme is envisioned to be an intramolecular Diels–Alder (IMDA) reaction of the tetraene **7** via an *endo*-transition state **7A** to construct the requisite tricyclic core while controlling the stereogenic centers at C3, C6, C14, and C15 in **6** (**7**→[**7A**]→**6**). The precursor **7** would be prepared directly by Stille-coupling of the vinyl iodide **8** and the vinylstannane **9**. The intermediate **8** should be accessed from the methyl acetylene **10** via hydrometallation/iodination and Wittig reaction. The intermediate **10** could in turn be derived through an intermolecular Diels–Alder reaction between Kitahara–Danishefsky's diene **11**[6] and the known enulose derivative **12**.[7]

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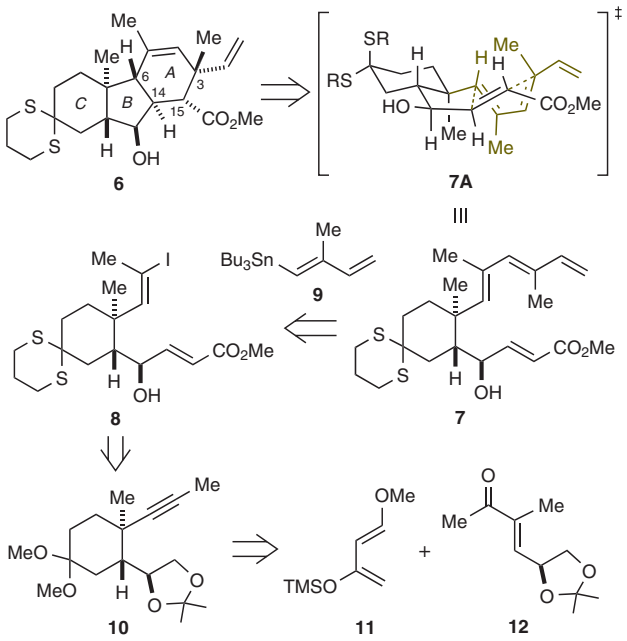
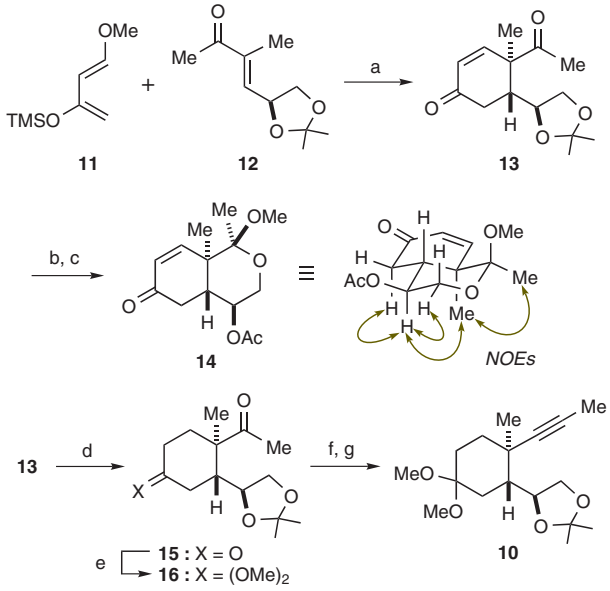


Scheme 1 Retrosynthetic analysis for the tricyclic core **6** (ABC-ring system) of GKK1032s.

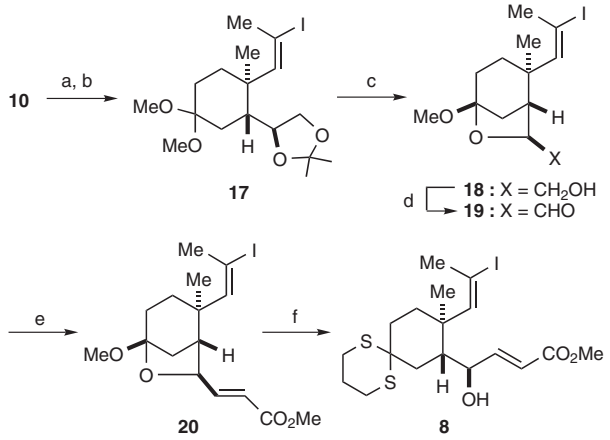
We initially pursued the synthesis of acetylene **10** as shown in Scheme 2. The intermolecular Diels–Alder reaction between Kitahara–Danishefsky's diene **11**[6] and the known enone **12**,[7] readily prepared from D-mannitol, provided the cyclohexenone **13**[8] in 60% yield as the sole isolated product. The stereostructure of **13** was proven by NOE studies of the bicyclic enone **14** derived from **13** by acid-catalyzed transacetalization followed by acetylation of the resulting alcohol. In this Diels–Alder reaction, the preferential approach of diene **11** to dienophile **12** took place from the opposite side of the bulky acetonide function, as previously reported by Ortuño et al.,[9] affording **13** as the sole isomer. Hydrogenation of the olefinic double bond in **13** followed by regioselective dimetylacetal formation of the resulting cyclohexanone **15** provided the dimethyl acetal **16** in 67% yield for the two steps. Compound **16** was further converted to the methyl acetylene **10** through a two-step sequence involving vinyl triflate formation[10] (84% yield) and base-induced elimination/methylation (73% yield).

Having obtained the key intermediate **10**, we next carried out the synthesis of the vinyl iodide **8** as shown in Scheme 3. Conversion of **10** to the corresponding vinyl iodide **17** under standard conditions, radical-mediated hydrostannylation/iodination (Bu_3SnH/AIBN; I_2),[11] Pd(0)-catalyzed hydrostannylation/iodination [Bu_3SnH/$Pd(PPh_3)_4$; I_2],[12] or hydrozirconation/iodination (Cp_2ZrHCl; I_2),[13] gave a poor yield of the product **17**. After several experiments, to our delight, we found that the use of Semmelhack's conditions[14] proved the most successful. Thus, treatment of **10** with a mixture of *n*-Bu_3SnH, $Pd(OAc)_2$, and PCy_3 in hexane at room temperature provided the corresponding (*E*)-vinyl stannane (58% yield) with complete regioselectivity, which was



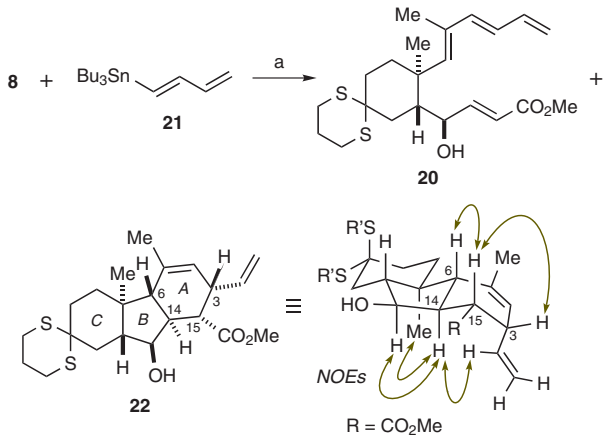
Scheme 2 Synthesis of the key intermediate **10**. *Reagents and conditions*: (a) toluene, 150 °C, 72 h, 60%; (b) *p*-TsOH, MeOH, reflux, 2 h, 77%; (c) Ac_2O, pyridine, r.t., 5 h, 94%; (d) H_2, 10% Pd/C, EtOAc, r.t., 12 h, 89%; (e) PPTS, MeOH, 0 °C, 2.5 h, 75%; (f) $KN(SiMe_3)_2$, THF; $PhNTf_2$, –78 °C, 2 h, 84%; (g) LDA, THF; MeI, 0 °C, 1 h, 73%.

then allowed to react with iodine to furnish the desired vinyl iodide **17** in 84% yield. In the next stage, introduction of an α,β-unsaturated ester moiety, which would serve as a dienophile in the designed key IMDA reaction, was performed. Thus, deprotection of the acetonide function in **17** by acid treatment led to the formation of the 5-membered acetal **18** in 82% yield. Swern oxidation of **18** followed by Wittig reaction of the resulting aldehyde **19** afforded the corresponding α,β-unsaturated ester **20** in 69% yield for the two steps. Finally, compound **20** was transformed to the requisite intermediate **8** in 98% yield via transacetalization by exposure to 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$.



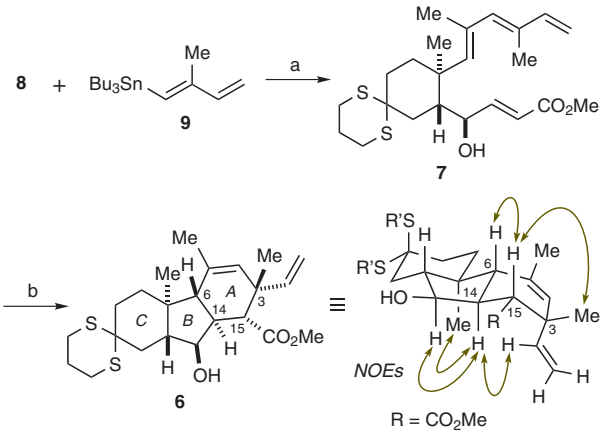
Scheme 3 Synthesis of the key intermediate **8**. *Reagents and conditions*: (a) *n*-Bu_3SnH, $Pd(OAc)_2$, PCy_3, hexane, r.t., 12 h, 58%; (b) I_2, CH_2Cl_2, 0 °C, 30 min, 84%; (c) PPTS, MeOH, reflux, 2 h, 82%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, 0 °C, 30 min; (e) $Ph_3P{=}CHCO_2Me$, toluene, r.t., 12 h, 69% (2 steps); (f) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –40 °C, 1 h, 98%.

With the key intermediate **8** in hand, as shown in Scheme 4, we next investigated the model studies for the construction of the tricyclic core structure **22**, which lacks a methyl substituent at the C3-position in the A-ring; the sequence involves Stille coupling of the vinyl iodide **8** with the known vinylstannane **21**[15] and subsequent key IMDA reaction of the product **20**. Since Corey et al. reported that Stille coupling was dramatically accelerated by the presence of CuCl,[16] we decided to employ the modified method of Corey et al. [$Pd(PPh_3)_4$, CuCl/LiCl, DMF–THF, r.t., 12 h], which led to the formation of the desired tetraene **20** (23% yield) and an unexpected cycloaddition product **22** (23% yield) as the sole diastereomer. NOE experiments of the cycloadduct **22** revealed that the newly generated stereochemistry at the C3-, C6-, C14-, and C15-positions was fully matched with that of GKK1032s. The formation of **22** under the mild Stille coupling conditions is particularly intriguing, and this phenomenon must be attributed to the structural nature inherent in the tetraene **20**.[17] Conversion of **20** to **22** (80% yield) was readily achieved by refluxing a solution of **20** in toluene.



Scheme 4 Synthesis of the tricyclic model compound **22**. *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (10 mol%), CuCl/LiCl, DMF–THF, r.t., 12 h, 23% for **20** and 23% for **22**.

Encouraged by these successful results, we finally conducted the synthesis of the targeted compound **6**, the tricyclic core of GKK1032s, as shown in Scheme 5. Thus, Stille coupling of the vinyl iodide **8** and the vinylstannane **9**[18] was carried out under the same conditions described for the model studies to furnish the desired tetraene **7**[19] in 60% yield. In this reaction, contrary to the model studies, no cycloadducts were isolated from the reaction mixture; therefore, the key IMDA reaction was executed by heating a solution of **7** in toluene in a sealed tube with a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) for 24 hours, giving rise to a 70% yield of decahydrofluorene **6**[20] as the isolated diasteromer.[21] The stereostructure of **6** was also confirmed by NOE experiments as shown in



Scheme 5 Synthesis of the tricyclic core **6** of GKK1032s. *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (10 mol%), CuCl/LiCl, DMF–THF, r.t., 12 h, 60%; (b) BHT, toluene, 120 °C, 24 h, 70%.

Scheme 5, which proved that the relative stereochemistry within **6** was fully identical with that of GKK1032s. The remarkable stereochemical outcome observed in the IMDA reaction can be rationalized by the predominant *endo*-transition state **7A** as depicted in Scheme 1.

In summary, we have succeeded in developing a facile synthetic route to the decahydrofluorene **6** via a highly diastereoselective IMDA reaction (**7**→[**7A**]→**6**), which is the first entry to a common tricylic core structure (ABC-ring system) of the GKK1032 family (**1**–**3**). The IMDA precursor **7** was efficiently synthesized by a method featuring stereoselective intermolecular Diels–Alder reaction of the siloxydiene **11** and the enone **12** to construct the functionalized C-ring (**11** + **12**→**13**) and Cu(I)-accelerated Stille coupling of the vinyl iodide **8** and the vinylstannane **9** to install the requisite triene moiety (**8** + **9**→**7**). Further investigation toward the total synthesis of GKK1032s (**1**–**3**) and pyrrocidines (**4**, **5**) is now in progress and will be reported in due course.

Acknowledgment

We are grateful to Dr. T. Mori (Tokyo Institute of Technology) for his assistance in MS spectra measurements.

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(8) **Data for 13**: Pale yellow oil $[\alpha]_D^{20}$ –55.7 (*c* 0.24, $CHCl_3$). IR (neat): 631, 733, 787, 852, 906, 920, 968, 1057, 1084, 1211, 1242, 1358, 1371, 1419, 1456, 1680, 1709, 1736, 2937, 2985 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 2.25 (s, 3 H), 2.49 (dd, *J* = 4.5, 17.1 Hz, 1 H), 2.60 (dd, *J* = 11.1, 17.1 Hz, 1 H), 2.71 (ddd, *J* = 2.7, 4.5, 11.1 Hz, 1 H), 3.36 (dd, *J* = 7.6, 8.2 Hz, 1 H), 4.01 (dd, *J* = 6.7, 8.2 Hz, 1 H), 4.07–4.15 (m, 1 H), 6.07 (d, *J* = 10.2 Hz, 1 H), 6.66 (d, *J* = 10.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 25.0, 25.8, 26.2, 34.3, 40.1, 53.4, 67.6, 74.3, 109.4, 129.0, 150.1, 198.0, 208.1. HR-FABMS: *m/z* calcd for $C_{14}H_{21}O_4$ $[(M + H)^+]$: 253.1440; found: 253.1448.

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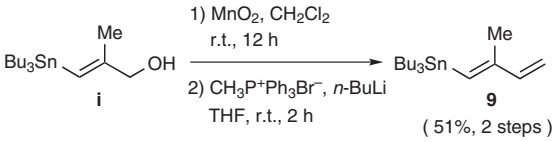
(17) Detailed discussions on this IMDA reaction will be presented in a full account.

(18) The vinylstannane **9** was prepared from the known compound **i**: (a) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139. (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47; via a two-step sequence of reactions as shown in Scheme 6.



Scheme 6

(19) **Data for 7**: Colorless viscous oil, $[\alpha]_D^{20}$ +18.2 (*c* 0.23, $CHCl_3$). IR (neat): 607, 648, 731, 779, 897, 908, 985, 1043, 1097, 1167, 1194, 1240, 1273, 1373, 1435, 1655, 1722, 2860, 2933, 2947, 2979, 3463 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.41–1.48 (m, 1 H), 1.50 (d, *J* = 4.8 Hz, 1 H), 1.83–2.04 (m, 4 H), 1.87 (d, *J* = 1.0 Hz, 3 H), 1.92 (d, *J* = 1.0 Hz, 3 H), 2.06–2.19 (m, 3 H), 2.24–2.30 (m, 1 H), 2.61–2.76 (m, 2 H), 2.81–2.98 (m, 2 H), 3.74 (s, 3 H), 4.59–4.65 (m, 1 H), 5.03 (d, *J* = 10.7 Hz, 1 H), 5.17 (d, *J* = 17.4 Hz, 1 H), 5.26 (br s, 1 H), 5.88 (br s, 1 H), 6.04 (dd, *J* = 1.9, 15.6 Hz, 1 H), 6.37 (dd, *J* = 10.7, 17.4 Hz, 1 H), 6.94 (dd, *J* = 4.1, 15.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 18.7, 21.0, 25.8, 26.0, 26.3, 32.0, 33.6, 34.6, 40.0, 44.5, 50.2, 51.7, 71.4, 112.2, 119.8, 133.1, 133.6, 137.7, 140.2, 142.0, 151.2, 166.8. HR-EIMS: *m/z* calcd for $C_{23}H_{34}O_3S_2$ (M^+): 422.1949; found: 422.1954.

(20) **Data for 6**: White solid, mp 161–166 °C, $[\alpha]_D^{20}$ +65.7 (*c* 0.45, $CHCl_3$). IR (neat): 607, 621, 688, 783, 804, 852, 908, 995, 1047, 1159, 1223, 1259, 1331, 1375, 1435, 1716, 2875, 2931, 3500 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.79 (s, 3 H), 1.28 (s, 3 H), 1.42–1.53 (m, 1 H), 1.69–1.83 (m, 3 H), 1.75 (s, 3 H), 1.89–2.00 (m, 3 H), 2.00–2.10 (m, 2 H), 2.11–2.18 (m, 1 H), 2.33 (dt, *J* = 8.3, 12.0 Hz, 1 H), 2.52 (dt, *J* = 13.4, 2.2 Hz, 1 H), 2.61 (d, *J* = 12.0 Hz, 1 H), 2.65–2.75 (m, 1 H), 2.77–2.87 (m, 2 H), 2.95–3.03 (m, 1 H), 3.68 (s, 3 H), 3.93–3.99 (m, 1 H), 4.85 (s, 1 H), 4.98 (dd, *J* = 1.5, 17.2 Hz, 1 H), 5.05, (dd, *J* = 1.5, 10.4 Hz, 1 H), 5.69 (dd, *J* = 10.4, 17.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 21.2, 25.9, 26.1, 26.4, 26.7, 34.5, 35.0, 35.3, 41.3, 42.4, 44.0, 50.3, 51.3, 52.3, 54.4, 55.5, 72.7, 114.5, 131.3, 135.4, 142.8, 174.8. HR-EIMS: *m/z* calcd for $C_{23}H_{34}O_3S_2$ (M^+): 422.1949; found 422.1950.

(21) In this IMDA reaction, a small amount (<10% yield) of unidentified products was generated along with the desired decahydrofluorene **6**.