Studies toward the Total Synthesis of GKK1032A$_2$, a Structurally Unique Antitumor Compound: Stereoselective Construction of the Tricarbocyclic System

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Abstract: The unique tricarbocyclic system in GKK1032A$_2$, an antitumor agent from *Penicillium* sp. GKK1032, was constructed in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analog.

Key words: antitumor agents, carbocycles, Diels–Alder reactions, natural products, stereoselective synthesis

GKK1032A$_2$ is a member of a novel class of antibiotic antitumor compounds recently isolated from *Penicillium sp.* GKK1032 (Figure 1).[1,2] These compounds exhibit potent activity against bacteria including drug-resistant strain, as well as antitumor activity against epithelioid cell HeLa S3.[1a] He et al. isolated pyrrocidines A and B, 3,6-bisepi-3-desmethyl analogues of GKK1032s, and reported that they showed similar bioactivity.[3] From a pharmaceutical point of view, these bioactivities make GKK1032 family an expecting candidate for a drug to control mutidrug-resistant *Staphylococcus aureus* and other nosocomial infections, and a new seed for anti-cancer drug. Structural feature of the compound was elucidated by NMR techniques and X-ray crystallographic analysis,[1b] which includes an unique 6-5-6 tricarbocyclic system and an unusual 13-membered macrocyclic ether containing 1,4-disubstituted phenyl moiety. Recently, Oikawa disclosed that the unique backbone of GKK1032A$_2$ is biosynthetically constructed from L-tyrosine and a nonaketide chain with five methyl groups.[4]

These biologically and synthetically attracting features of GKK1032 family prompted us to embark on the total synthesis of GKK1032A$_2$.

The synthetic plan is shown in Scheme 1. The macrocyclic moiety of **1** could be constructed from an aldehyde **2** via carbon chain elongation followed by ring-closure. The cyclohexene ring in **2** is expected to be formed by Diels–Alder reaction between a diene **3** and an appropriate dienophile which may occur from the upper face of the diene taking advantage of a steric effect of the aromatic ring. The diene **3** would be readily accessible from a known bicyclic ketone **4**[5] available with high optical purity. We describe herein a method to construct the tricarbocyclic system of GKK1032s in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analogue **4**.

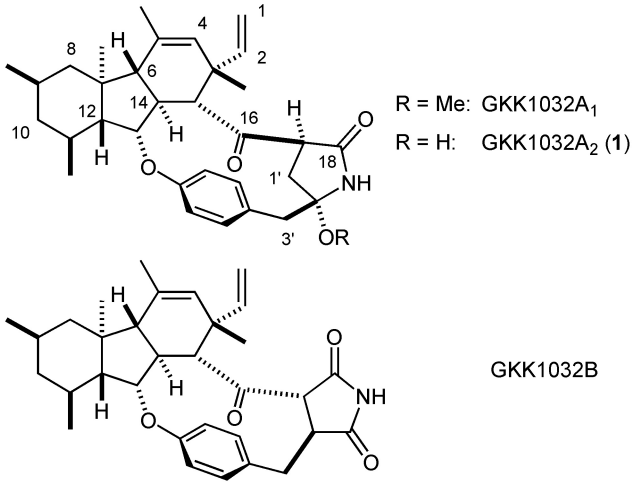
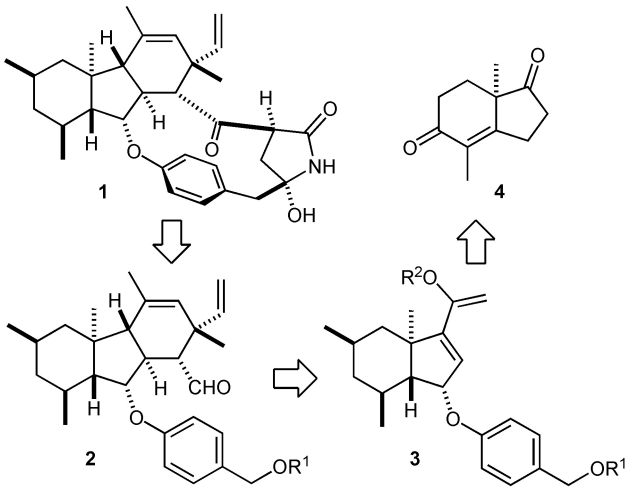


Figure 1 Structures of GKK1032 family.



Scheme 1 Retrosynthetic analysis of GKK1032A$_2$.

The bicyclic ketone **4** was regio- and stereoselectively reduced and protected with TBS group[5] to afford an enone **5** (Scheme 2). For the *trans* selective reduction of 6–5

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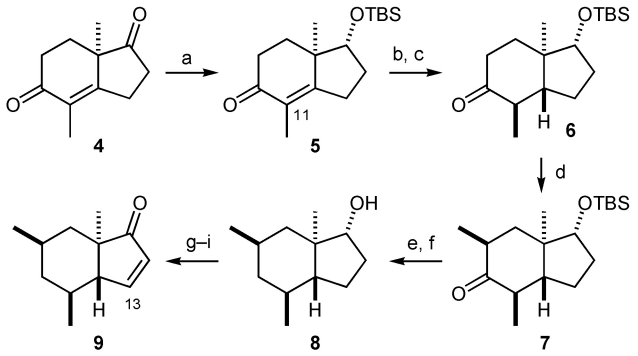
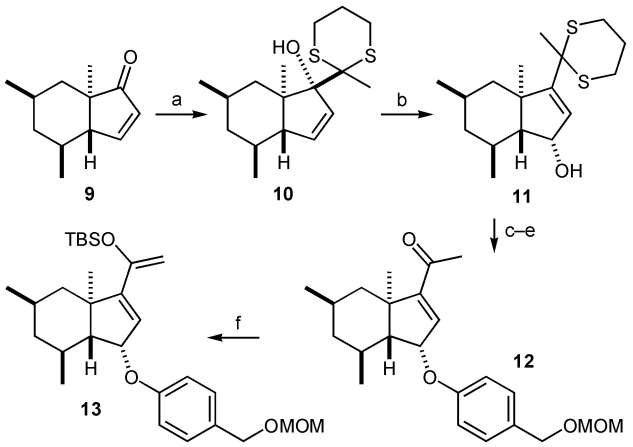
bicyclic enone related to **5**, we preferred a catalytic hydrogenation procedure convenient for multi-gram scale preparation at the early stage of the total synthesis. On the catalytic hydrogenation of this type of compounds, it was reported that the larger is a substituent at α-position of the enone [corresponding to C(11)-Me in **5**, GKK1032A$_2$ numbering], the higher *trans* selectivity is observed,[6] though unsubstituted substrates gave *cis* major product.[7,8] Indeed, the hydrogenation of **5** proceeded with high *trans* selectivity in THF to afford **6** via a subsequent epimerization under basic conditions. Use of the dry solvent was essential to achieve the high *trans* selectivity, otherwise the selectivity was markedly decreased, and in some case inverted. Methylation of **6** under kinetic conditions followed by epimerization produced a ketone **7** in good yield. A secondary alcohol **8** obtained by conventional deoxygenation[9] of **7** was converted into an enone **9** via Swern oxidation[10] and dehydrogenation under Tsuji's conditions.[11]



Scheme 2 *Reagents and conditions*: a) ref. 5; b) H_2, Pd/C, THF, 0 °C, 1 d, *trans*/*cis* = ca.9:1; c) NaOEt, EtOH, reflux, 6 h, 77% (2 steps); d) LDA, THF, –78 °C, 3 h, then MeI, –78 °C to r.t., 85%; e) 1,2-ethanedithiol, BF_3·OEt_2, neat, 0 °C to r.t., 1 d, 85%; f) Raney Ni (W-2), EtOH, reflux, 14 h, 76%; g) $(COCl)_2$, DMSO, Et_3N, –78 to 0 °C, 1 h, 93%; h) LDA, THF, –78 °C, 3 h, then TMSCl; i) 10 mol% $Pd(OAc)_2$, allyl carbonate, MeCN, reflux, 67% (2 steps).

For the stereoselective introduction of an oxygen functionality at C(13)-position, we decided to utilize Krafft's procedures: they reported a suprafacial 1,3-rearrangement of the hydroxyl group of tertiary allylic alcohol obtained by addition of 2-lithio-2-methyl-1,3-dithiane to cyclopentenone moiety in a steroid derivative under dilute acidic conditions.[12] Their protocol worked well also in our case: Addition of the lithiodithiane to the enone **9** took place selectively from the opposite side of the angular methyl group and a subsequent treatment with dilute sulfuric acid afforded allylic alcohol **11** in excellent stereoselectivity (Scheme 3). Introduction of the aryl ether was effectively achieved by using aromatic S_N2 reaction between a fluoroarene chromium complex and an alkoxide of **11**,[13] followed by decomplexation with CAN.[14] The deprotection of the dithiane turned out to be somewhat troublesome, probably due to a steric factor and the instability of the aryl ether moiety under the reaction conditions.[15] After several trials, it was found that application of Stork's method[16] as well as Panek's protocol[17]

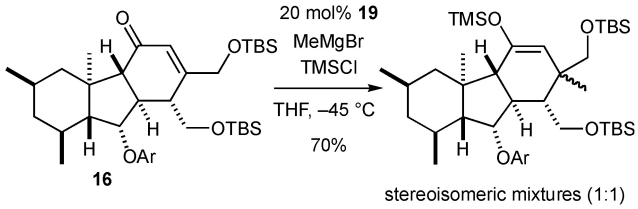


Scheme 3 *Reagents and conditions*: a) 2-lithio-2-methyl-1,3-dithiane, THF, –78 to –23 °C, 5 h, 97%; b) 0.5% H_2SO_4, aq THF, 0 °C to r.t., 1 d, 77% (3 recycles), >20:1 stereoselectivity; c) NaH, η^6-4-$FC_6H_4CH_2OMOM$-$Cr(CO)_3$, THF, reflux, 7 h, 81%; d) CAN, $NaHCO_3$, MeCN, –23 °C, 20 min, 82%; e) Dess–Martin periodinane, MeCN–CH_2Cl_2–H_2O, r.t., 39 h, 70%; f) KHMDS, TBSCl, THF–HMPA, –78 °C to r.t., 95%.

gave enone **12** in an acceptable yield. The diene **13** was readily prepared by usual procedure from **12**.

Thus, the stage was set for the formation of the third 6-membered ring. In refluxing toluene, the [4+2]cycloaddition of dimethyl fumarate to the diene **13** took place selectively from the opposite side of OAr to afford the desired **14a** as a major product together with a small amount of its epimer **14b** (Scheme 4). The stereochemistry of each product was determined by NOE experiments. Reduction of **14a** to a diol followed by treatment with TBAF afforded a thermodynamically most favorable *trans*-fused ketone. Protection of the diol moiety with TBS provided **15**, which was converted into an enone **16**. A stereoselective introduction of methyl on the C(3)-position to form a quaternary carbon was a next critical aspect of our synthetic study. While usual procedures for conjugate addition (e.g., Me_2CuLi,[18] MeMgBr–cat.Cu(I)–TMSCl[19]) did not work with the enone **16**, a Cu(II)–salicylidene–iminato complex **19** catalyzed reaction[20] effected the addition to afford methylation product in good yield. However, no stereoselection was observed (Equation 1), and we had to modify the structure of the substrate appropriate for the π-facial selection.

After various examinations, we found that the cyclic silyl ether **17**, easily available from **16** via a protective group manipulation,[21] was the substrate of choice for the stereo-



Equation 1

selective 1,4-addition. When **17** was subjected to the above conditions, the addition product **18** was obtained as a sole product (Scheme 4). The complete stereoselectivity observed in this conjugate addition could be explained by considering the structural feature of **17** shown in Figure 2.

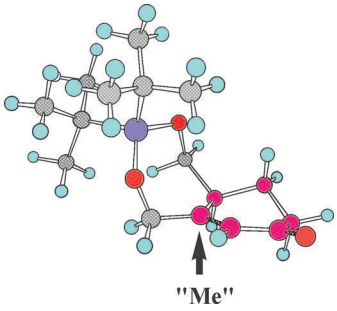
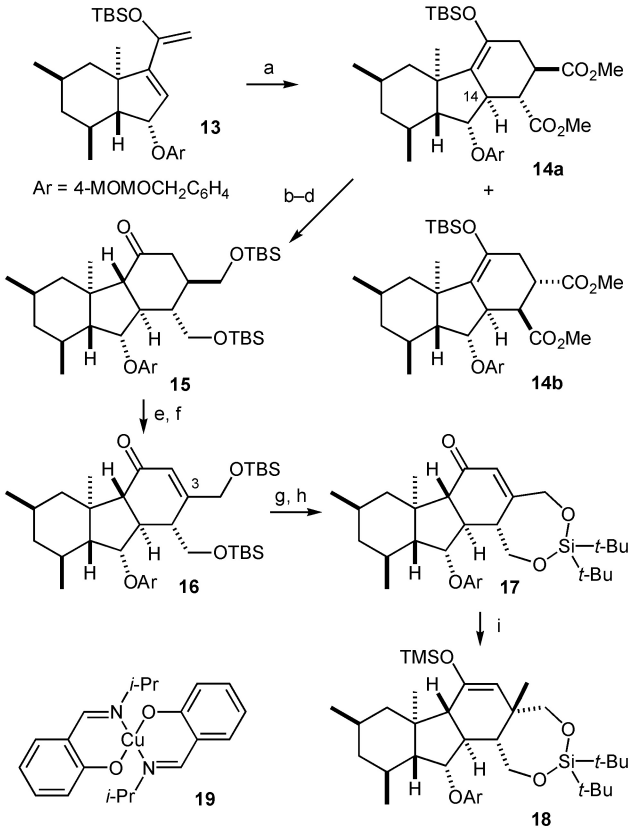


Figure 2 An optimized structure of the right half of **17**.



Scheme 4 *Reagents and conditions*: a) dimethyl fumarate, toluene, reflux, 10 h, **14a** 83%, **14b** 17%; b) $LiBH_4$, THF–MeOH, 0 °C to r.t., 1 d, 91%; c) TBAF, THF, 0 °C to r.t., 2 h; d) TBSCl, imidazole, DMF, r.t., 1 h, 97% (2 steps); e) LDA, TMSCl, THF, –78 °C, 3 h; f) $Pd(OAc)_2$, MeCN, 50 °C, 10 h; g) TBAF, THF, 0 °C to r.t., 2 h; h) $(t\text{-}Bu)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, –78 to –45 °C, 4 h, 58% (based on **15**); i) MeMgBr, TMSCl, 10 mol% **19**, THF, –45 °C, 44 h, 84% (single stereoisomer).

The trimethylsiloxy group in **18** was replaced with methyl group via three sequential steps, silyl–lithium exchange,[22] triflation with Comins reagent,[23] Pd(0)–Me_2Zn reagents,[24] affording **20** (Scheme 5). Compound **20** carries all required functionalities in the tricarbocyclic core of GKK1032s with correct stereochemistry. Since **20** was isolated as a crystalline compound, the relative configuration was unambiguously determined by X-ray crystallographic analysis (Figure 3).[25]

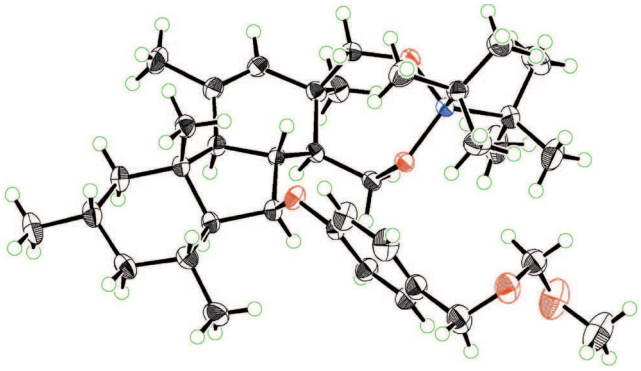
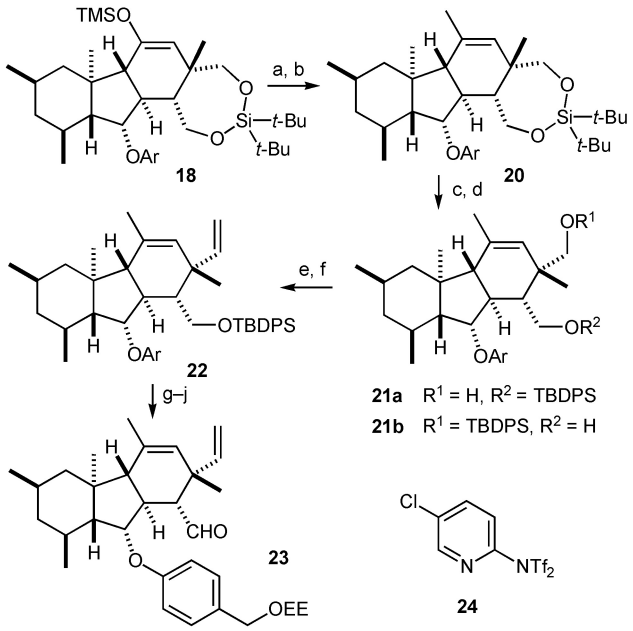


Figure 3 ORTEP drawing of **20**.

After deprotection of the silylene in **20** with TBAF, regioselective TBDPS ether formation was nicely carried out under low temperature conditions to give **21a** in preference to **21b**. Oxidation of the remaining hydroxy group in **21a** followed by Wittig reaction[26] led to **22**, which was converted into aldehyde **23** via usual protecting group manipulation. Thus, we established a highly stereoselective synthetic route from the known ketone **4** to the aldehyde **23**, which could be a useful common intermediate in the total synthesis of GKK1032 family.



Scheme 5 *Reagents and conditions*: a) MeLi, THF, –78 °C to r.t., 2 h, then **24**, –78 °C, 16 h, 86%; b) Me_2Zn, $Pd(PPh_3)_4$, THF, 0 °C to r.t., 28 h, 95%; c) TBAF, THF, r.t., 20 h; d) TBDPSCl, Et_3N, 10 mol% DMAP, CH_2Cl_2, –78 °C to –45 °C, 4 h, **21a** 80%, **21b** 13%; e) $(COCl)_2$, DMSO, Et_3N, –78 °C to 0 °C, 1 h, 95%; f) $MePh_3PBr$, BuLi, THF, 0 °C, 2 h, 96%; g) 2 M HCl, aq THF, 35 °C, 8 h, 95% (3 recycles); h) ethyl vinyl ether, 10 mol% PPTS, CH_2Cl_2, r.t., 3 h; i) TBAF, MS 4 Å, THF, 40 °C, 17 h, quant. (2 steps); j) SO_3·pyridine, Et_3N, DMSO, r.t., 1.5 h, 89%.

We are now investigating the total synthesis of GKK1032s, and will describe this in the near future.

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(25) Crystallographic data for **22**: formula, $C_{37}H_{60}O_2Si$; FW, 612.94; crystal system, orthorhombic; space group, $P2_12_12_1$; a = 11.7726 (4) Å, b = 12.9543 (4) Å, c = 23.5023 (8) Å; V = 3584.2 (2) Å^3; Z = 4; T = 170 K; D_{calcd} = 1.136 g cm^{-1}; $\lambda(MoK_\alpha)$ = 0.71070 Å; $R1$ = 0.0418 [I>2σ(I)]; $wR2$ = 0.1082; GOF(F^2) = 1.064.
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