

# Studies toward the Total Synthesis of GKK1032A<sub>2</sub>, a Structurally Unique Antitumor Compound: Stereoselective Construction of the Tricarbobicyclic System

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Received 15 April 2005

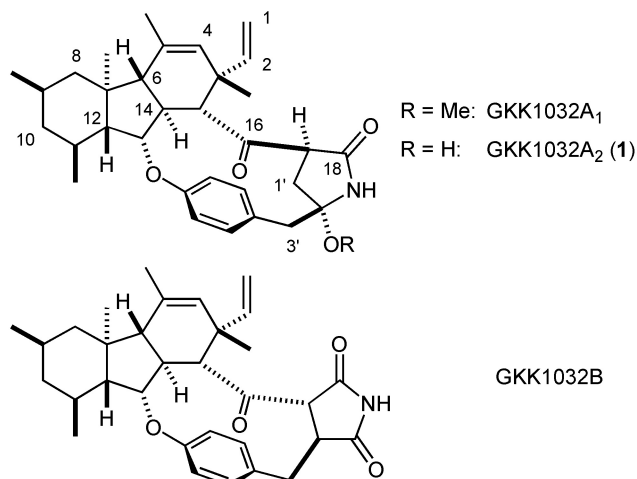
**Abstract:** The unique tricarbobicyclic system in GKK1032A<sub>2</sub>, an antitumor agent from *Penicillium* sp. GKK1032, was constructed in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analog.

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

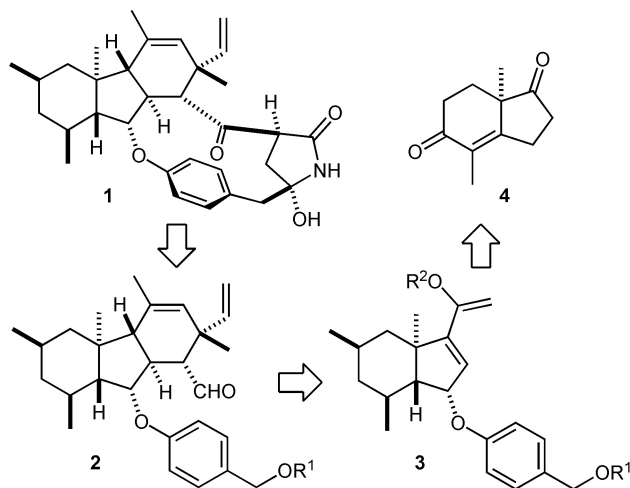
GKK1032A<sub>2</sub> is a member of a novel class of antibiotic antitumor compounds recently isolated from *Penicillium* sp. GKK1032 (Figure 1).<sup>1,2</sup> These compounds exhibit potent activity against bacteria including drug-resistant strain, as well as antitumor activity against epithelioid cell HeLa S3.<sup>1a</sup> He et al. isolated pyrrocidines A and B, 3,6-bisepi-3-desmethyl analogues of GKK1032s, and reported that they showed similar bioactivity.<sup>3</sup> From a pharmaceutical point of view, these bioactivities make GKK1032 family an expecting candidate for a drug to control multidrug-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,<sup>1b</sup> which includes an unique 6-5-6 tricarbobicyclic system and an unusual 13-membered macrocyclic ether containing 1,4-disubstituted phenyl moiety. Recently, Oikawa disclosed that the unique backbone of GKK1032A<sub>2</sub> is biosynthetically constructed from L-tyrosine and a nonaketide chain with five methyl groups.<sup>4</sup>

These biologically and synthetically attracting features of GKK1032 family prompted us to embark on the total synthesis of GKK1032A<sub>2</sub>.

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** available with high optical



**Figure 1** Structures of GKK1032 family.

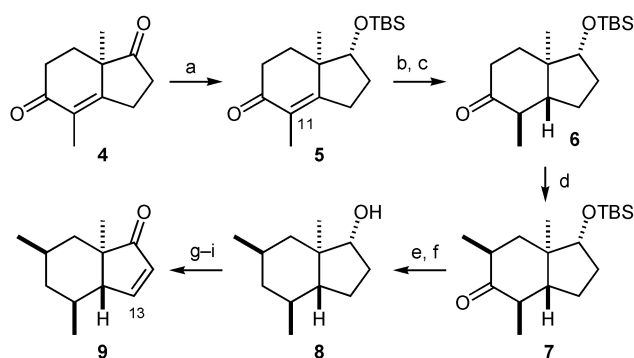


**Scheme 1** Retrosynthetic analysis of GKK1032A<sub>2</sub>.

purity. We describe herein a method to construct the tricarbobicyclic system of GKK1032s in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analogue **4**.

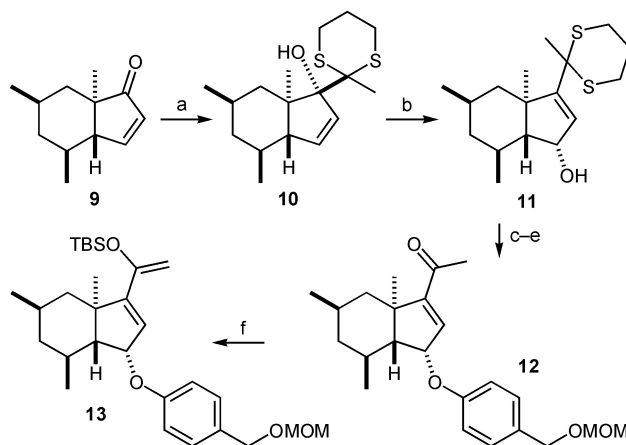
The bicyclic ketone **4** was regio- and stereoselectively reduced and protected with TBS group<sup>5</sup> to afford an enone **5** (Scheme 2). For the *trans* selective reduction of 6–5

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  $\alpha$ -position of the enone [corresponding to C(11)-Me in **5**, GKK1032A<sub>2</sub> numbering], the higher *trans* selectivity is observed,<sup>6</sup> though unsubstituted substrates gave *cis* major product.<sup>7,8</sup> 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<sup>9</sup> of **7** was converted into an enone **9** via Swern oxidation<sup>10</sup> and dehydrogenation under Tsuji's conditions.<sup>11</sup>



**Scheme 2** Reagents and conditions: a) ref. 5; b) H<sub>2</sub>, 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<sub>3</sub>·OEt<sub>2</sub>, neat, 0 °C to r.t., 1 d, 85%; f) Raney Ni (W-2), EtOH, reflux, 14 h, 76%; g) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, -78 to 0 °C, 1 h, 93%; h) LDA, THF, -78 °C, 3 h, then TMSCl; i) 10 mol% Pd(OAc)<sub>2</sub>, 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.<sup>12</sup> 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<sub>N</sub>2 reaction between a fluoroarene chromium complex and an alkoxide of **11**,<sup>13</sup> followed by decomplexation with CAN.<sup>14</sup> 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.<sup>15</sup> After several trials, it was found that application of Stork's method<sup>16</sup> as well as Panek's protocol<sup>17</sup>

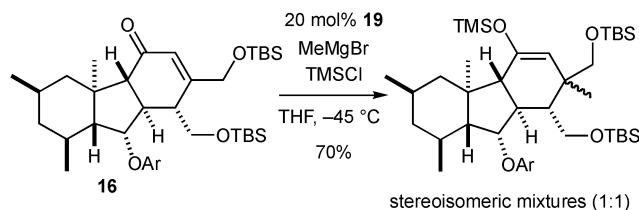


**Scheme 3** Reagents and conditions: a) 2-lithio-2-methyl-1,3-dithiane, THF, -78 to -23 °C, 5 h, 97%; b) 0.5% H<sub>2</sub>SO<sub>4</sub>, aq THF, 0 °C to r.t., 1 d, 77% (3 recycles), >20:1 stereoselectivity; c) NaH,  $\eta^6$ -4-FC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OMOM-Cr(CO)<sub>3</sub>, THF, reflux, 7 h, 81%; d) CAN, NaHCO<sub>3</sub>, MeCN, -23 °C, 20 min, 82%; e) Dess-Martin periodinane, MeCN-CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O, 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<sub>2</sub>CuLi,<sup>18</sup> MeMgBr-cat.Cu(I)-TMSCl<sup>19</sup>) did not work with the enone **16**, a Cu(II)-salicylidene-iminato complex **19** catalyzed reaction<sup>20</sup> 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  $\pi$ -facial selection.

After various examinations, we found that the cyclic silyl ether **17**, easily available from **16** via a protective group manipulation,<sup>21</sup> 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.

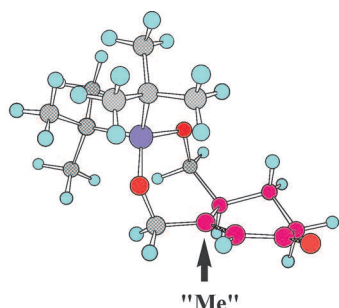
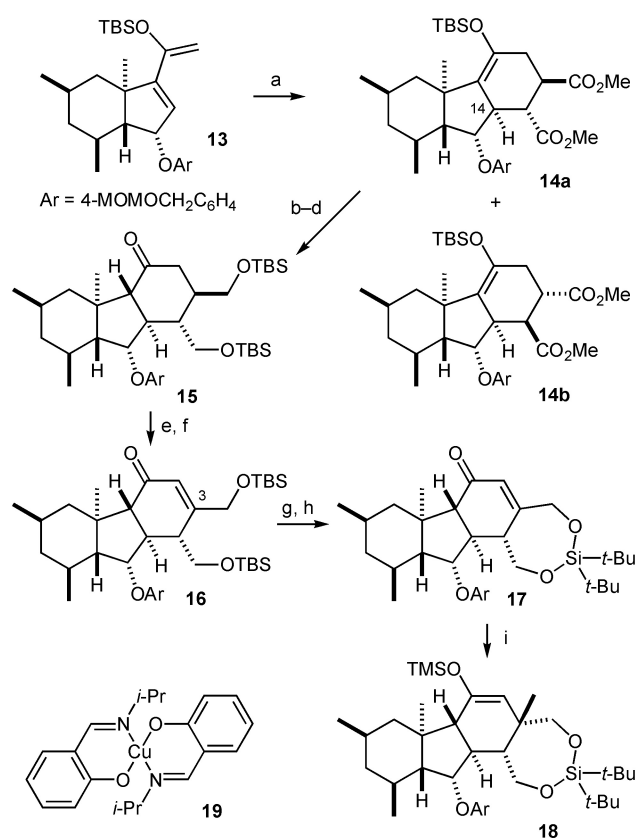


Figure 2 An optimized structure of the right half of **17**.



**Scheme 4** Reagents and conditions: a) dimethyl fumarate, toluene, reflux, 10 h, **14a** 83%, **14b** 17%; b)  $\text{LiBH}_4$ , 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)  $\text{Pd}(\text{OAc})_2$ , MeCN, 50 °C, 10 h; g) TBAF, THF, 0 °C to r.t., 2 h; h)  $(t\text{-Bu})_2\text{Si}(\text{OTf})_2$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , –78 to –45 °C, 4 h, 58% (based on **15**); i)  $\text{MeMgBr}$ , 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,<sup>22</sup> triflation with Comins reagent,<sup>23</sup>  $\text{Pd}(0)$ – $\text{Me}_2\text{Zn}$  reagents,<sup>24</sup> 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).<sup>25</sup>

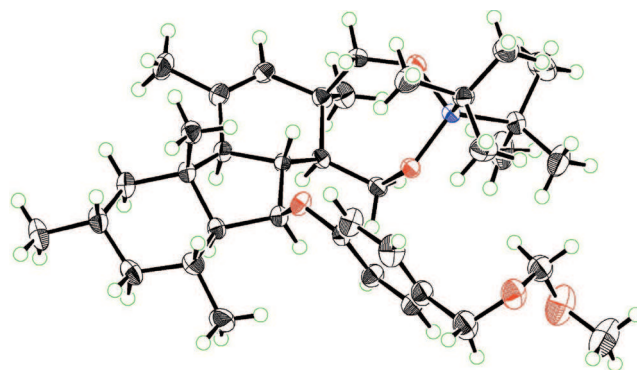
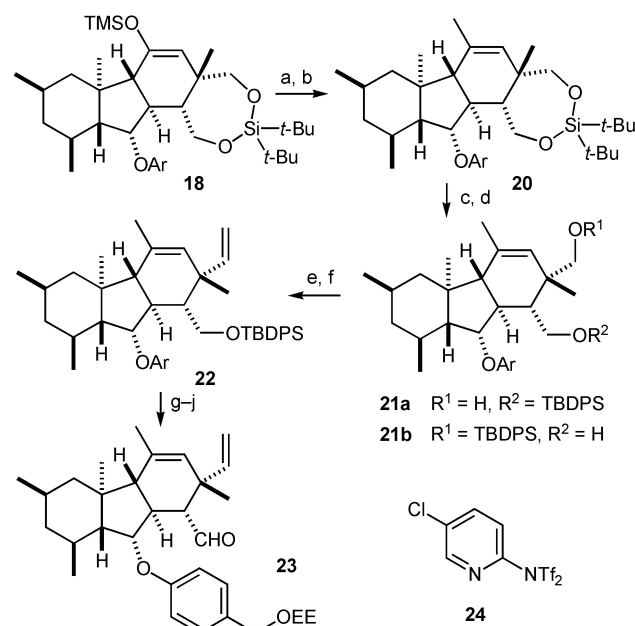


Figure 3 ORTEP drawing of **20**.

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<sup>26</sup> 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)  $\text{Me}_2\text{Zn}$ ,  $\text{Pd}(\text{PPh}_3)_4$ , THF, 0 °C to r.t., 28 h, 95%; c) TBAF, THF, r.t., 20 h; d) TBDPSCl,  $\text{Et}_3\text{N}$ , 10 mol% DMAP,  $\text{CH}_2\text{Cl}_2$ , –78 °C to –45 °C, 4 h, **21a** 80%, **21b** 13%; e)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ , –78 °C to 0 °C, 1 h, 95%; f)  $\text{MePh}_2\text{PBr}$ , 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,  $\text{CH}_2\text{Cl}_2$ , r.t., 3 h; i) TBAF, MS 4 Å, THF, 40 °C, 17 h, quant. (2 steps); j)  $\text{SO}_3$ –pyridine,  $\text{Et}_3\text{N}$ , DMSO, r.t., 1.5 h, 89%.

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

### Acknowledgment

The authors acknowledge Dr. M. Minoura in Department of Chemistry, Faculty of Science, Kitasato University, for X-ray crystallographic analysis of **20**.

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- (25) Crystallographic data for **22**: formula, C<sub>37</sub>H<sub>60</sub>O<sub>2</sub>Si; FW, 612.94; crystal system, orthorhombic; space group, P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>; *a* = 11.7726 (4) Å, *b* = 12.9543 (4) Å, *c* = 23.5023 (8) Å; *V* = 3584.2 (2) Å<sup>3</sup>; *Z* = 4; *T* = 170 K; *D*<sub>calcd</sub> = 1.136 g cm<sup>-3</sup>; λ(MoK<sub>α</sub>) = 0.71070 Å; *R*<sub>1</sub> = 0.0418 [*I* > 2σ(*I*)]; *wR*<sub>2</sub> = 0.1082; GOF(*F*<sup>2</sup>) = 1.064.
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