Studies toward the Total Synthesis of GKK1032A₂, a Structurally Unique Antitumor Compound: Stereoselective Construction of the Tricarbocyclic System

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Abstract: The unique tricarbocyclic system in GKK1032A₂, 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

GKK1032A₂ 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 S3.3 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 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, 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 GKK1032A₂ 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 GKK1032A₂.

The synthetic plan is shown in Scheme 1. The macrocyclic moiety of I 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 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.

The bicyclic ketone 4 was regio- and stereoselectively reduced and protected with TBS group5 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 numbering], the higher trans selectivity is observed, though unsubstituted substrates gave cis major product. 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 of 7 was converted into an enone 9 via Swern oxidation and dehydrogenation under Tsuji’s conditions.

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 cyclopentone moiety in a steroid derivative under dilute acidic conditions. 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$_2$N$_2$ reaction between a fluoroarene chromium complex and an alkoxide of 11, followed by decomplexation with CAN. 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. After several trials, it was found that application of Stork’s method as well as Panek’s protocol 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$_2$CuLi, 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, was the substrate of choice for the stereo-

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$_2$SO$_4$, aq THF, 0 °C to r.t., 1 d, 77% (3 recycles), >20:1 stereoselectivity; c) NaH, η$^4$-FC$_3$H$_7$CHOMOM-Cr(CO)$_5$, THF, reflux, 7 h, 81%; d) CAN, NaHCO$_3$, MeCN, –23 °C, 20 min, 82%; e) Dess–Martin periodinane, MeCN–CH$_2$Cl$_2$–H$_2$O, r.t., 39 h, 70%; f) KHMS, TBSCI, THF–HMPA, –78 °C to r.t., 95%.

Scheme 2 Reagents and conditions: a) ref. 5; b) H$_2$, Pd/C, THF, 0 °C, 1 d, trans/cis = ca.9:1; c) NaOMe, 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-ethanediol, BF$_3$-EtO$_2$, neat, 0 °C to r.t., 1 d, 85%; f) Raney Ni (W-2), EtOH, reflux, 14 h, 76%; g) (COCl)$_2$, DMSO, Et,N, –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).

Equation 1

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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](image)

**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) TBDSCI, 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-
Bu)$_2$Si(OTf)$_2$, 2,6-lutidine, CH$_2$Cl$_2$, −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$_2$Zn 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 configura-
tion was unambiguously determined by X-ray crys-
tallographic analysis (Figure 3).$^{25}$

![Figure 3](image)

**Figure 3** ORTEP drawing of 20.

After deprotection of the silylene in 20 with TBAF, regio-
selective 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 manipula-
tion. 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$_2$Zn, Pd(PPh$_3$)$_4$, THF, 0 °C to r.t.,
28 h, 95%; c) TBAF, THF, r.t., 20 h; d) TBDPSiCl, Et$_3$N, 10 mol%
DMAP, CH$_2$Cl$_2$, −78 °C to −45 °C, 4 h, 21a 80%, 21b 13%; e)
(COCI)$_2$, DMSO, Et$_3$N, −78 °C to 0 °C, 1 h, 95%; f) Me$_2$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, CH$_2$Cl$_2$, r.t., 3 h; i)
TBAF, MS 4 Å, THF, 40 °C, 17 h, quant. (2 steps); j) SO$_3$·pyridine,
Et$_3$N, DMSO, r.t., 1.5 h, 89%.

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

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References


(25) Crystallographic data for 22: formula, C_{12}H_{20}O_{2}Si; FW, 612.94; crystal system, orthorhombic; space group, P2_{1}2_{1}2_{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_{calc} = 1.136 g cm^{-3}; \lambda(MoK_{α}) = 0.71070 Å; R1 = 0.0418 [I>2\sigma(I)]; wR2 = 0.1082; GOF(F^{2}) = 1.064.