Model Studies towards the Total Synthesis of GKK1032s, Novel Antibiotic Anti-Tumor Agents: Enantioselective Synthesis of the Alkyl Aryl Ether Portion of GKK1032s

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Abstract: An enantioselective synthesis of an alkyl aryl ether portion of GKK1032s, novel antibiotic anti-tumor agents, was achieved via Mitsunobu reaction between a sterically congested indenol derivative and a *p*-substituted phenol derivative. The indenol derivative, the key substrate for the Mitsunobu reaction, was efficiently synthesized starting from the known indanone derivative through regio- and stereoselective methylation, Saegusa oxidation, and carbonyl transposition as the pivotal steps.

Key words: GKK1032s, antibiotic, anti-tumor agent, natural products synthesis, Mitsunobu reaction, Saegusa oxidation

GKK1032A$_1$ (**1**) and A$_2$ (**2**, Figure 1), isolated from a strain of *Penicillium sp.* in 2001, exhibit prominent biological properties such as antimicrobial and anti-tumor activities.[1,2] Pyrrocidines A (**3**) and B (**4**), subsequently isolated from the culture broth of a fungus, display antimicrobial activity against Gram-positive bacteria including drug-resistant strains.[3] Structurally, these natural products consist of a tricyclic decahydrofluorene nucleus (ABC-ring) appended to an unusual 13-membered macrocycle containing ether, phenyl, pyrrolidinone, and carbonyl functionalities. These rather unique structure features together with the attractive biological properties have made GKK1032s and pyrrocidines exceptionally intriguing and timely targets for total synthesis. Synthetic studies of these natural products have been recently disclosed by several research groups;[4] however, no total synthesis has been reported to date.

In the course of our ongoing project directed towards the total synthesis of optically active GKK1032s, we have recently reported the first entry to the tricyclic decahydrofluorene nucleus (ABC-ring, **5**),[5] which features a highly diastereoselective intramolecular Diels–Alder reaction as the key step (cf. **7** → **5**, Scheme 1). To forward the next stage of the projected total synthesis, we were strongly required to develop a method for the construction of the characteristic alkyl aryl ether portion of GKK1032s. In this paper, we wish to report our further investigation concerning an efficient and facile synthesis of the model compound **6** (Figure 1), which contains the alkyl aryl ether portion as well as the fully substituted C-ring moiety present in GKK1032s and pyrrocidines.

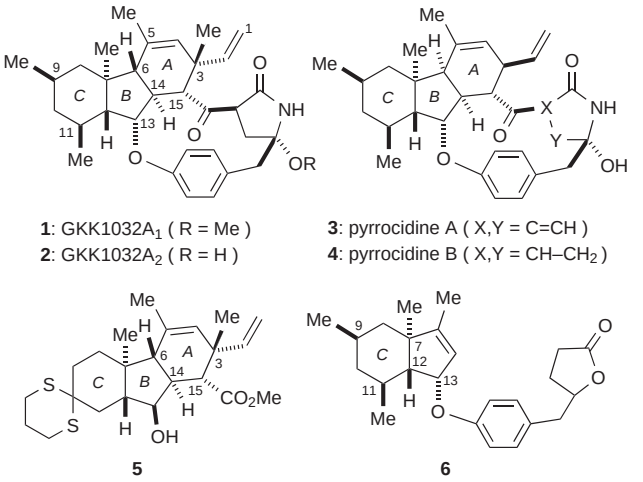
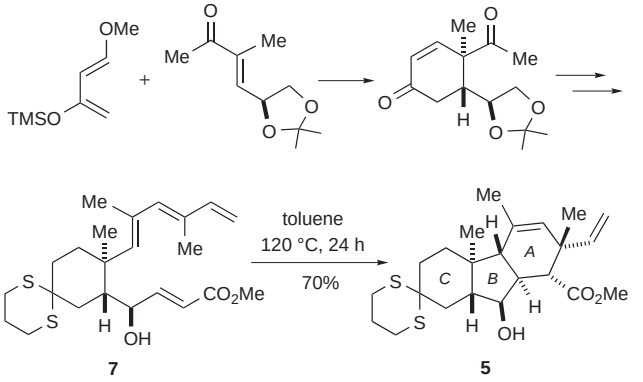


Figure 1 Structures of GKK1032A$_1$ (**1**), A$_2$ (**2**), pyrrocidines A (**3**), B (**4**), the tricyclic decahydrofluorene nucleus **5**, and the alkyl aryl ether portion **6**

The synthetic plan for the model compound **6** is outlined in Scheme 2. The key feature in this scheme is envisioned to be an uncommon Mitsunobu reaction[6] between the indenol **8** and *p*-substituted phenol **9** to construct the requisite asymmetric carbon center at the C13 position



Scheme 1 Outline of our developed synthetic route to the tricyclic decahydrofluorene nucleus **5**

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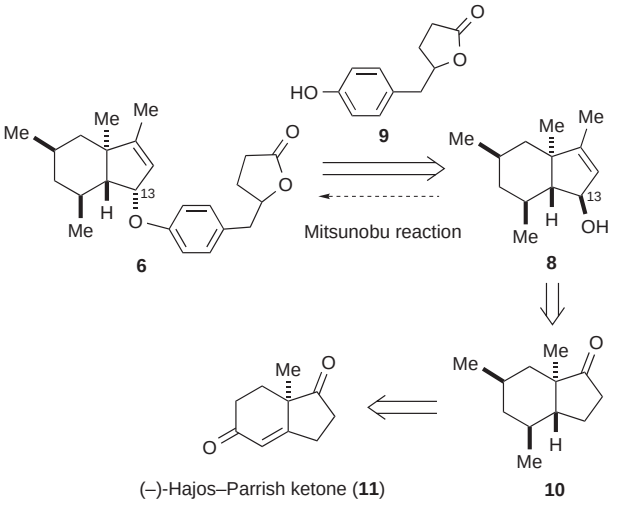
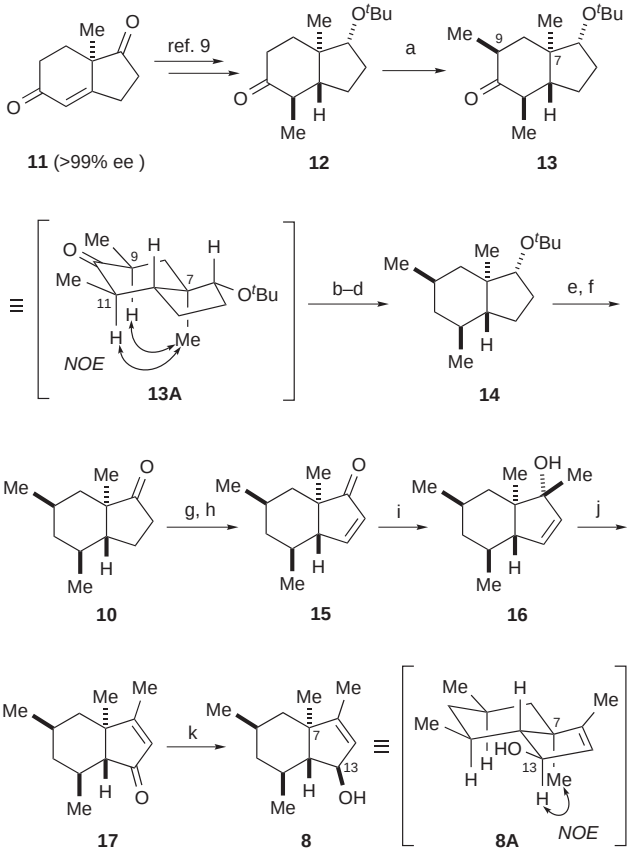
(**8** + **9** → **6**). This coupling reaction is considerably challenging at a synthetic chemistry level because the C13 hydroxy group present in the indenol **8** is placed in a sterically congested position. The precursor **8** would be available from the indenone **10** via Saegusa oxidation[7] followed by carbonyl transposition and reduction. The intermediate **10** would be derived from the enantiomerically pure (–)-Hajos–Parrish ketone (**11**;[8] >99% ee) through regio- and stereoselective methylation.



Scheme 2 Synthetic plan for the model compound **6**

At first, as shown in Scheme 3, we pursued the synthesis of the indenol **8**, the substrate for the key Mitsunobu reaction, starting from the known enantiomerically pure ketone **12**[9] readily prepared from **11**. Regio- and stereoselective methylation of **12** was successfully achieved by treatment with lithium diisopropylamide (LDA) followed by addition of iodomethane, which provided the requisite dimethylketone **13** as a single diastereomer in 93% yield. The configuration of the newly formed C9 stereocenter in **13** was confirmed by NOESY experiments as depicted in **13A**, where clear NOE interactions between the angular methyl group (C7–Me) and C9–H, C11–H were observed, respectively. Removal of the carbonyl function in **13** was carried out by sodium borohydride reduction followed by deoxygenation of the resulting alcohol by employing the Barton–McCombie protocol.[10] The desired decarbonylation product **14** was obtained in 81% yield for the three steps. After deprotection of the *tert*-butyl group in **14** under acidic conditions, the liberated hydroxy group was then oxidized with Dess–Martin periodinane[11] to afford the indanone **10** in 88% overall yield. Installation of the enone system was next conducted by applying the Saegusa procedure.[7] Thus, treatment of **10** with LDA and subsequent addition of trimethylsilyl chloride (TMSCl) provided the corresponding silyl enol ether, which was then oxidized with palladium(II) acetate to give the desired indenone **15** in 77% yield for the two steps. The carbonyl transposition of **15** was effectively achieved via a two-step sequence involving 1,2-addition of methyl lithium and oxidation of the resulting allyl alcohol **16** with pyridinium chlorochromate (PCC), furnishing the desired product **17** (57%, 2 steps). Finally, the carbonyl group in **17** was steroselectivelly reduced under the Luche conditions[12] to provide the allyl alcohol **8**[13] as a single diastereomer in 82% yield.[14] The configuration of the newly generated C13 stereocenter was determined by NOE experiments, wherein the clear interaction between C13-H and C7-Me was observed as pictured in **8A**.

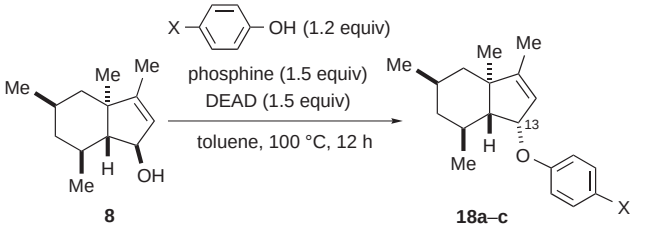


Scheme 3 Synthesis of the intermediate **8**. *Reagents and conditions*: (a) LDA, THF, –78 °C; MeI, –50 °C to 0 °C, 2 h, 93%; (b) $NaBH_4$, EtOH, –78 °C, 1 h, quant.; (c) $NaN(SiMe_3)_2$, CS_2, –78 °C, 30 min, MeI, –78 °C, 30 min, 90%; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 12 h, 90%; (e) concd HCl, dioxane, reflux, 1 h; (f) Dess–Martine periodinane, CH_2Cl_2, r.t., 2 h, 88% (2 steps); (g) LDA, THF, –78 °C, 1 h; TMSCl, –78 °C to r.t., 1 h; (h) $Pd(OAc)_2$, MeCN, 50 °C, 3 h, 77% (2 steps); (i) MeLi, Et_2O, r.t., 1.5 h, quant.; (j) PCC, CH_2Cl_2, r.t., 12 h, 57%; (k) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0 °C, 1 h, 82%

Having obtained the key intermediate **8** in an efficient way, we next focused our attention on the synthesis of the targeted model compound **6** by employing the Mitsunobu reaction.[6] As a preliminary experiment, we examined the Mitsunobu reaction between **8** and simple *p*-substituted phenols as shown in Table 1. When the reaction of **8** with *p*-methoxyphenol was carried out under conventional Mitsunobu conditions [diethyl azodicarboxylate (DEAD), triphenylphosphine, THF, r.t.], the expected alkyl ether **18a** was not detected in the reaction mixture, and the unreacted starting material **8** was recovered unchanged. After several trials, to our delight, we found that the reaction proceeded by heating at 100 °C in toluene for 12 hours;

the expected coupling product **18a** was produced in 11% yield (entry 1). Employing tributylphosphine instead of triphenylphosphine, the reaction gave **18a** in an improved yield (41%, 13α:13β = 10:1;[15] entry 2). Additionally, the reaction of **8** with *p*-nitrophenol and *p*-cresol gave the corresponding alkyl aryl ethers **18b** and **18c** in 41% yield and 43% yield, respectively (entries 3 and 4). The newly formed C13 stereocenter of the Mitsunobu coupling products **18a**,**c** was confirmed by NOE experiments. Thus, as shown in Figure 2, clear NOE correlations between C13–H and C12–H, C11–Me were observed, while no NOE interaction was observed between C13–H and C7–Me.

Table 1 Mitsunobu Reaction of the Indenol **8** with some *p*-Substituted Phenols



8 **18a–c**

Entry	X	Phosphine	Product	Ratio (13α:13β)[a]	Yield (%)[b]
1	OMe	PPh_3	**18a**	10:1	11
2	OMe	P(*n*-Bu)$_3$	**18a**	10:1	41
3	NO_2	P(*n*-Bu)$_3$	**18b**	10:1	41
4	Me	P(*n*-Bu)$_3$	**18c**	10:1	43

[a] Determined by 500 MHz ^{1}H NMR spectroscopy.
[b] Isolated yield by column chromatography on silica gel.

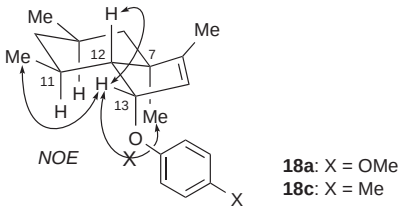
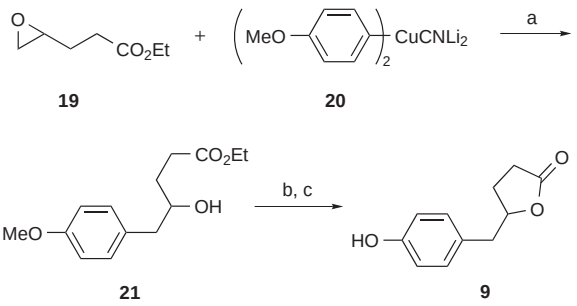
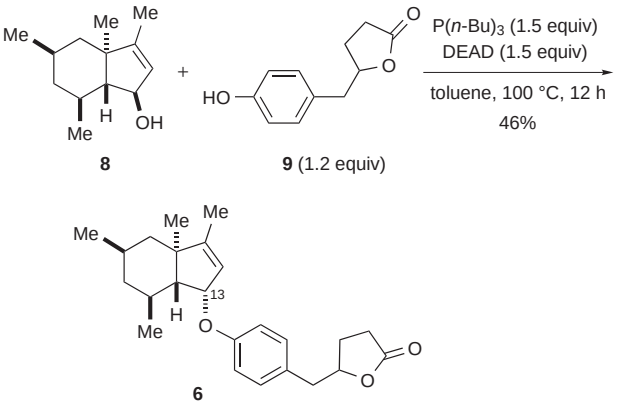


Figure 2 Selected NOESY correlation of **18a**,**c**

Having succeeded in the Mitsunobu reaction between **8** with some *p*-substituted phenolic compounds, we next investigated the synthesis of the targeted molecule **9** based on the model studies. Toward this end, as shown in Scheme 4, the required *p*-substituted phenol derivative **9** containing the δ-lactone ring was initially prepared starting from the known epoxide **19**.[16] Treatment of **19** with the aryl cuprate reagent **20** (prepared from *p*-bromoanisole, *n*-BuLi, and CuCN) afforded the desired coupling product **21** in 60% yield. Acid-catalyzed lactonization of **21** followed by deprotection of the methyl group by exposure to boron tribromide in dichloromethane at 0 °C, provided the requisite phenol derivative **9**[17] in 91% yield for the two steps. The key Mitsunobu reaction between the allyl alcohol **8** and the phenol derivative **9** (1.2 equiv) was finally achieved under the same conditions described for the model studies to furnish the targeted compound **6**[18] in 46% yield (13α:13β = 10:1[15]).



Scheme 4 Synthesis of the *p*-substituted phenol derivative **9**. *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$, –78 °C, 30 min, 60%; (b) camphor-10-sulfonic acid, benzene, reflux, 1 h, 91%; (c) BBr_3, CH_2Cl_2, 0 °C, 24 h, quant.



Scheme 5 Synthesis of the model compound **6**

In summary, we have developed a facile method for the synthesis of the alkyl aryl ether portion **6** of GKK1032s in an enantioselective manner by employing Mitsunobu reaction of the functionalized indenol **8** and *p*-substituted phenol **9** (**8** + **9** → **6**; Scheme 5). The key substrate **8** was efficiently synthesized starting from the known ketone **12**; the method features a regio- and stereoselective methylation (**12** → **13**), Saegusa oxidation (**10** → **15**), and carbonyl transposition (**15** → **16** → **17**) as the crucial steps. Further investigation towards the total synthesis of GKK1032s and pyrrocidines based on the present studies is now in progress and will be reported appropriately in due course.

Acknowledgment

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(13) **Data for 8.**
Colorless viscous oil, $[\alpha]_D^{20}$ –52.2 (*c* 0.70 $CHCl_3$). IR (neat): 644, 808, 993, 1039, 1049, 1140, 1205, 1377, 1439, 1456, 2839, 2868, 2906, 2949, 3317 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.51–0.61 (m, 1 H), 0.83 (s, 3 H), 0.85–0.94 (m, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 1.00–1.08 (m, 1 H), 1.23 (d, *J* = 7.4 Hz, 1 H), 1.55–1.62 (m, 1 H), 1.65 (t, *J* = 1.8 Hz, 3 H), 1.68–1.75 (m, 1 H), 1.76–1.89 (m, 2 H), 4.47–4.54 (m, 1 H), 5.27 (t, *J* = 1.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.3, 19.4, 20.7, 22.8, 28.3, 29.5, 43.3, 45.8, 48.0, 66.5, 77.7, 127.8, 152.6. HRMS (EI): *m*/*z* calcd for $C_{13}H_{22}O$ [M^+]: 192.0786; found: 192.0790.

(14) This remarkable stereoselectivity can be rationalized by the consideration that the hydride attack occurred exclusively from α-face of the carbonyl group under an influence of stereoelectronic effect, which may involve the so-called ‘product development control’.

(15) Since separation of 13α-form and 13β-form was very difficult, the ratio was estimated by ^1H NMR (500 MHz) spectroscopy.

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(17) **Data for 9.**
White solid, mp 101–104 °C. IR (KBr): 652, 677, 818, 843, 972, 985, 1171, 1186, 1223, 1516, 1743, 3342 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89–1.99 (m, 1 H), 2.21–2.30 (m, 1 H), 2.31–2.40 (m, 1 H), 2.41–2.51 (m, 1 H), 2.89 (dd, *J* = 14.2, 5.9 Hz, 1 H), 2.97 (dd, *J* = 14.2, 6.0 Hz, 1 H), 4.67–4.75 (m, 1 H), 5.05 (s, 1 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9, 28.7, 40.4, 81.1, 115.5 (2 C), 127.7, 130.7 (2 C), 154.8, 177.5. HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}O_3$ [M^+]: 194.1671; found: 194.1667.

(18) **Data for 6.**
Colorless viscous oil, $[\alpha]_D^{20}$ +129.5 (*c* 0.16 $CHCl_3$). IR (neat): 607, 634, 806, 937, 1005, 1045, 1173, 1227, 1240, 1373, 1508, 1736, 1774, 2910, 2949 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.54–0.65 (m, 1 H), 0.82 (t, *J* = 12.0 Hz, 1 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.18 (s, 3 H), 1.30 (dd, *J* = 11.6, 5.1 Hz, 1 H), 1.63 (dd, *J* = 11.6, 4.1 Hz, 1 H), 1.71 (s, 3 H), 1.80–1.88 (m, 1 H), 1.88–2.07 (m, 3 H), 2.18–2.27 (m, 1 H), 2.30–2.50 (m, 2 H), 2.85 (dd, *J* = 14.1, 6.4 Hz, 1 H), 2.99 (dd, *J* = 14.1, 5.8 Hz, 1 H), 4.64–4.73 (m, 1 H), 4.82–4.87 (m, 1 H), 5.67 (s, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.09 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.8, 19.4, 22.0, 22.9, 26.7, 27.0, 28.1, 28.7, 40.40 (1/2 C), 40.39 (1/2 C), 43.1, 45.6, 48.2, 60.4, 78.896 (1/2 C), 78.868 (1/2 C), 81.1, 115.695 (1/2 C × 2), 115.703 (1/2 C × 2), 121.883 (1/2 C), 121.892 (1/2 C), 127.104 (1/2 C), 127.111 (1/2 C), 130.3 (2 C), 157.840 (1/2 C), 157.831 (1/2 C), 159.6, 177.155 (1/2 C), 177.172 (1/2 C). HRMS–FAB: *m*/*z* calcd for $C_{24}H_{33}O_3$ [M + H]$^+$: 369.2430; found: 369.2465.