Diels-Alder reactions using 4,7-dioxygenated indanones as dienophiles for regioselective construction of oxygenated 2,3-dihydrobenz[f]indenone skeleton

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Abstract
Regioselective construction of 4,8,9-trioxygenated 2,3-dihydrobenz[f]indenones, key intermediates for the synthesis of kinamycin antibiotics, was achieved via Diels-Alder reactions (DAR) using 4,7-dioxygenated indanone-type compounds as dienophiles. Reaction of indanetrione with 1-methoxybutadiene gave a 1:1 mixture of undesired 4,5,9-trioxygenated 2,3-dihydrobenz[f]indenone and [4.4.3]propellane. The addition of Lewis acid did not affect the product ratio, whereas the use of the 6-bromoindanetrione exclusively afforded the latter propellane. On the other hand, DAR of benzyne derived from bromoindan and furan gave 5,8-epoxy-2,3-dihydrobenz[f]indenone, which was subjected to acid-induced ring opening to give 2,3-dihydrobenz[f]indenone with undesired 4,5,9-trioxy functions.

Background
Kinamycins, isolated from Streptomyces murayamaensis sp. nov. Hata et Ohtani in 1970 [1-3], have attracted attention due to their antibiotic and antitumor activities [7-10]. These compounds had been originally characterized as cyanamides 1 with a linearly-fused 6-6-5-6 membered ring system [11,12]; however, the structure was revised to diazaoalkanes 2 by spectroscopic means [13,14] and by total synthesis [15-17] (Figure 1). In our total synthesis of methyl-kinamycin C (3) [21], regioselective synthesis of 4,8,9-trioxygenated 2,3-dihydrobenz[f]indenone 4 [22] was a key issue, which was achieved via C ring construction with intramolecular Friedel-Crafts reaction of naphthalenepropanoic acid 5 (path A, Scheme 1) [23]. However, the utilization of a stoichiometric amount of expensive silver salt for the synthesis of bromonaphthalene 6 [24] hampered large-scale synthesis of 4. Towards a solution to this problem, we planned the synthesis of 4 via A-ring construction by DAR of indanone-type compounds and oxygenated dienes: i.e. 1) DAR of indanetrione 8 and 1-methoxy-1,3-butadiene (7) (path B; quinone route) [28]; 2) regioselective ring-opening of 5,8-epoxy-2,3-dihydrobenz[f]indenone 11.
derived from benzyne 10 and furan (9) (path C, benzyne route). Now we report that both of the methods are effective for the construction of the 2,3-dihydrobenz[f]indenone skeleton, but not for the regioselective synthesis of the desired 4,8,9-trioxygenated ones.

Results and Discussion

In the quinone route, we designed several indanetriones to modulate steric and electronic factors; i.e. 1,4,7-indanetrione 8, the 6-brominated quinone 12, and the corresponding 4-monoacetals 13 and 14 (Scheme 2). Intramolecular Friedel-Crafts reaction of 2,5-dimethoxybenzenepropanoic acid (15) and the 4-brominated derivative 16 [31], by a procedure modified from the synthesis of 4 [23], afforded the corresponding indanones 17 and 18. Cerium ammonium nitrate (CAN) oxidation [32] of indanone 17 smoothly afforded indanetrione 8, but attempts with bromoindanone 18 resulted in no reaction even under reflux. Utilization of a milder oxidant phenyliodosyl bis(trifluoroacetate) (PIFA) [33] for the oxidation of phenolic indanone 20, derived from 18 by selective demethylation with magnesium iodide (MgI₂) [34], gave bromoquinone 12 after modification of the workup protocol without aqueous sodium bicarbonate. The PIFA oxidation of phenols 19 [35] and 20 in the presence of methanol gave the corresponding monoacetals 13 and 14.

DAR of indanetrione 8 and 1-methoxy-1,3-butadiene (7) in dichloromethane (CH₂Cl₂) proceeded smoothly at −16 °C to give a 1 : 1 mixture of 2,3-dihydrobenz[f]indenone 21 and [4.4.3]propellane 22, produced by participation of the double bond at the ring junction in 8 (entry 1 in Table 1). Both compounds were obtained as single diastereoisomers. The former was determined as an undesired 5-methoxy derivative 21, the structure of which was deduced by HMBC correlations and NOE enhancement (Figure 2a). The latter structure 22 was also determined by HMBC and NOE experiments (Figure 2b); however, the relative configuration of the carbon connected to the methoxy group could not be determined because of lacking NOE data. Next, the effect of Lewis acid on the regioselectivity was examined. At first, zinc chloride (ZnCl₂), an effective cata-

**Figure 1:** The structure of kinamycins.

**Scheme 1:** Retrosynthesis of kinamycins.
**Table 1: DARs of dienophiles 8, 12-14 and diene 7.**

| Entry | Dienophile | Solvent | Additive | Conditions | Results |
|-------|------------|---------|----------|------------|---------|
| 1     | 8          | CH₂Cl₂  | -        | −16 °C, 4 h | 21: 22 = 47%:42% a |
| 2     | 8          | CH₂Cl₂  | ZnCl₂ (0.14 eq) | −78 °C, 4 h | 21: 22 = 8%:1 b |
| 3     | 8          | CH₂Cl₂  | ZnCl₂ (1 eq)  | −78 °C, 2 h | 21 (9%) a |
| 4     | 8          | CH₂Cl₂  | BF₃·OEt₂ (0.14 eq) | −78 °C, 2 h | 21: 22 = ca. 0.8:1 b, c |
| 5     | 8          | CH₂Cl₂  | BF₃·OEt₂ (1 eq) | −78 °C, 2 h | CM d |
| 6     | 12         | CH₂Cl₂  | -        | −16 °C, 4 h | 23 (89%) a |
| 7     | 12         | CH₂Cl₂  | BF₃·OEt₂ (0.14 eq) | −78 °C, 2 h | 23 (57%) a |
| 8     | 13         | CH₂Cl₂  | -        | rt, 8 h | NR e |
| 9 f   | 13         | toluene  | -        | 120 °C, 9 h | 19 (21%): 22 (16%) a |
| 10    | 14         | CH₂Cl₂  | -        | rt, 6 h | 23 (4%) a |
| 11    | 14         | CH₂Cl₂  | ZnCl₂ (0.20 eq) | rt, 2 h | 20 (15%): 23 (8%) a |

a) Isolated yield(s). b) Estimated by 1H NMR of crude product. c) 21 (4%) and 22 (11%) were isolated after column chromatography. d) A complex mixture. e) No reaction. f) Performed in a sealed tube.

**Scheme 2: Synthesis of quinones 8 and 12 and the acetals 13 and 14. Reagents and conditions:**
- a) P₂O₅, CH₃SO₃H, CH₂Cl₂ or CHCl₃ (67% for 17, 71% for 18); b) bromine, 1,4-dioxane, H₂O, rt, 2 h (68%); c) CAN, CH₃CN, H₂O, 0 °C, 30 min (65%); d) MgI₂·6H₂O, benzene, Dean-Stark (81% for 19, 96% for 20); e) PIFA, H₂O, CH₃CN, rt, 30 min (86%); f) PIFA, CH₂OH, CH₃CN, 0 °C (74% for 13, 92% for 14).

Next, instead of ZnCl₂, which is only slightly soluble in CH₂Cl₂, boron trifluoride etherate (BF₃·OEt₂) was applied as a soluble Lewis acid; however, similar results were obtained to those with ZnCl₂ (entries 4, 5). Interestingly, when bromoquinone 12 was reacted under the conditions of entry 1, lyst on DAR of benz[fl]indenone and Danishefsky-type diene [21], was chosen. Addition of a catalytic amount of ZnCl₂ at −78 °C did not affect the regioselectivity (entry 2). An increase in the amount of ZnCl₂ led to the formation of a complex mixture containing a small amount of propellane 22 (entry 3).
Table 2: Effect of base on DAR of in situ formed benzyne 10 and furan (9).

| Entry | Base (equiv) | Furan (equiv) | Conditions          | 26 (%)<sup>a</sup> | 25 Recovery (%)<sup>a</sup> |
|-------|--------------|---------------|---------------------|---------------------|-----------------------------|
| 1<sup>b</sup> | NaNH<sub>2</sub> (4.0) | 16 | 50 °C, 14 h | 3 | 79 |
| 2<sup>c</sup> | NaNH<sub>2</sub> (4.0) | 16 | 100 °C, 250 W, 150 psi, 1 h | 12 | 69 |
| 3 | LDA (1.0) | 14 | −78 °C – rt, 3 h | 25 | 53 |
| 4 | LDA (2.0) | 14 | −78 °C – rt, 3.5 h | 24 | 27 |
| 5 | LDA (1.0) | 2 | −78 °C – rt, 3.5 h | 30 | 39 |
| 6 | (CH<sub>3</sub>)<sub>2</sub>Zn(TMP)Li (2.2) | 2 | −78 °C – rt, 3.5 h | NR<sup>d</sup> | |
| 7 | LiTMP (1.0) | 2 | −78 °C – rt, 2.5 h | NR<sup>d</sup> | |

<sup>a</sup>Isolated yield. <sup>b</sup>Performed in a sealed tube. <sup>c</sup>Under microwave irradiation. <sup>d</sup>No reaction.

Next, synthesis of 2,3-dihydrobenz[f]indenone via a benzyne route was examined by treatment of bromoindanone acetal 25, prepared from bromoindanone 18, with a base in the presence of furan (9) (Scheme 3). Application of Giles’ protocol [41] using sodium amide as a base in the presence of a large excess amount (ca. 15 equivalents) of furan (9) in THF gave 5,8-epoxy-2,3-dihydrobenz[f]indenone 26 in 3% yield together with recovery of the starting 25 (79%) (entry 1 in Table 2). The yield was still low (12%) under microwave irradiation (entry 2). The use of lithium disopropynamide (LDA) [42] in THF slightly increased the yield of 26 to 25% (entry 3). Although no improvement was observed after increasing the quantity of the base.

DAR at the ring junction proceeded exclusively to give bromopropellane 23 in high yield as the sole product (entry 6). The yield was slightly reduced and the regioselectivity was not affected in the reaction in the presence of a catalytic amount of BF<sub>3</sub> · OEt<sub>2</sub> (entry 7).

We next turned to the use of quinone monoacetals 13 and 14 as dienophiles [36]. No adduct was formed on reaction of 13 in CH<sub>2</sub>Cl<sub>2</sub> without a catalyst at room temperature (rt) (entry 8), whereas refluxing in toluene gave deprotected propellane 22 (16%) together with phenol 19 (23%), a synthetic precursor of 13 (entry 9). Stirring bromoquinone monoacetal 14 in CH<sub>2</sub>Cl<sub>2</sub> at rt yielded only a small amount of propellane 23 (entry 10). The regioselectivity and the yield were not improved by the addition of ZnCl<sub>2</sub> from which the phenol 20 and propellane 23 were isolated in low yields as conversion products (entry 11). The desired 4,8,9-trioxogenated 2,3-dihydrobenz[f]indenone-type compound 24 was not obtained in any of the experiments.

Scheme 3: DAR of benzyne 10 and furan (9). Reagents and conditions: a) ethylene glycol, PPTS, benzene, reflux, 17 h (89%); b) conc. HCl, methanol, reflux, 19 h (50%); c) conc. HCl, methanol, THF, reflux, 38 h (39%, with recovery of 11 in 42%).
base (entry 4), the yield was slightly improved to 30% on decreasing the quantity of furan (9) to two equivalents (entry 5). Bases derived from tetramethylpiperidine (TMP) [43] were not effective (entries 6, 7). Thus, the desired improvement of the yield was not observed for the synthesis of the 5,8-epoxybenz[f]indene derivative 26; nevertheless, the ring-opening step was examined. Treatment of 26 with hydrochloric acid in a mixture of methanol and THF after deprotection of the ketal unit [41] afforded a ring-opened product 27 in 39% yield with recovery of epoxy ketone 11 (42%). The structure of 27 was determined to be the 5-hydroxylated compound, not 8-oxygenated isomer 28, by HMBC and NOE experiments (Figure 3).

In the former quinone route, the regioselectivity on the introduced methoxy group in 2,3-dihydrobenz[f]indenone was examined. 4,5,9-Trioxygenated 2,3-dihydrobenz[f]indenone derivative 21 was exclusively formed on DAR of indanetrione 8 and diene 7 because of selective activation of the C6 carbon due to the presence of additional cross conjugation between the C1 and the C4 carbonyl groups (TS-A, Figure 4). Semiempirical calculation [44] of molecular orbitals of quinone 8 supported this proposal, in which a larger LUMO coefficient (0.295) was obtained at C6 compared with C5 (0.244, Figure 5a). On the other hand, the reverse of the selectivity was expected when Lewis acid is coordinated with two carbonyls at C1 and C7 to positively activate the C5 carbon (TS-B, Figure 4); however, the addition of a catalytic amount of Lewis acid did not affect the regioselectivity. Similar reversal of the selectivity was also expected on using a quinone monoacetal to mask the ketone functionality at the 4 position (TS-C); however, the desired 2,3-dihydrobenz[f]indenone-type compound was not obtained.

On the other hand, propellane-type product 22 was obtained as a by-product in DAR of 8. In the case of reaction of bromoquinone 12, propellane 23 was the sole product. Larger coefficients at C3a and C7a carbons compared with those of C5 and C6 ones supported this phenomenon (Figure 5a). The steric bulk of the bromine atom in 12 can assist the selective formation of 23 (Figure 5b).

In the latter benzyne strategy, 4,5,9-trioxygenated derivative 27 was formed as a sole product in the acid-catalyzed ring-opening of 5,8-epoxyindanone 11. Giles et al. [41] reported the acid-induced ring opening of 1,4-epoxy-5-methoxynaphthalene (29) to furnish 5-methoxy-1-naphthol (32) via selective C4-O bond cleavage due to the electron-donating effect of the 5-methoxy group (Scheme 4). Therefore, in 5,8-epoxy-2,3-dihydrobenz[f]indenone system 11, regioselective C5-O bond cleavage was expected by the aid of the 4-methoxy group due to the deactivation of the 9-methoxy group by conjugation with the carbonyl at the 1 position to afford desired 4,8,9-trioxygenated compound 28 (Path C, Scheme 5). However, protonation of the carbonyl oxygen of 11 could yield a C-4a carbocation 37 with conjugation to oxocarbenium ion 36 (path D). In this case, generation of the desired 4,8,9-trioxygenated 2,3-dihydrobenz[f]indenone 28 seemed unlikely due to unfavorable adjacent dicaticonic intermediate 38 after C5-O bond cleavage of 37. Thus, formation of an alternative dication 39 through C8-O bond cleavage of 37 is favored instead to give undesired 4,5,9-trioxygenated 2,3-dihydrobenz[f]indenone 27.

**Conclusion**

DAR approaches toward regioselective construction of 4,8,9-trioxygenated 2,3-dihydrobenz[f]indenone skeleton were examined. Unfortunately undesired 4,5,9-trioxygenated derivat-
Figure 5: Representative LUMO coefficients of quinones 8 and 12 (a) and their reaction courses with diene 7 (b).

Scheme 4: The proposed mechanism for the acid-induced ring opening of epoxynaphthalene 29 by Giles et al. [19].

Scheme 5: Supposed reaction pathways for the acid-induced ring opening of 11.

Supporting Information

Supporting Information File 1
Experimental part
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