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Synthetic studies on kinamycin antibiotics: elaboration of a highly oxygenated D-ring

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Abstract

The synthesis of the model compound of kinamycin antibiotics, which possesses correct relative configurations at C(1)−C(4) on the D-ring, is reported. The key steps involve a Diels–Alder reaction of an indenone and a Danishefsky-type diene, and stereoselective construction of a tetraoxygenated D-ring.

Kinamycins were isolated from the culture broth of *Streptomyces murayamaensis* sp. nov. Hata and Ohtani by Omura et al.[1] and are strongly active against gram-positive bacteria but less so against gram-negative bacteria. The structures had been characterized as benzo[*b*]carbazoloquinone *N*-cyanamides (**1**)[2] with a highly oxygen-functionalized D-ring. Kinamycins were found to be biosynthetically derived from dehydrorabelomycin (**3**) through prekinamycin.[3]

Problems still remain for the determination of the substituent pattern at 11 position in the C ring (atoms X and Y). The reported data of IR (2150 cm^{-1}) and ^{13}C NMR (δ_C 78 ppm) for kinamycins poorly agreed with those of typical *N*-cyanoindoles (2237–2245 cm^{-1}, δ_C 105–108 ppm).[4] Thus, Gould et al.[5] and Dmitrienko et al.[6] independently reported the revision of the *N*-cyanamide structures (**1** for kinamycins, **4** for prekinamycin) to diazonium structures (**2** for kinamycins, **5** for prekinamycin), based on further X-ray crystallographic studies and synthetic work for **4**, respectively. However, in spite of the accepted structures **2** for kinamycins, Gould doubted the structure **5** for prekinamycin due to some discrepancies between a synthetic compound **5** and a natural prekinamycin (Fig. 1).[7]

These situations led us try to determine the structures of kinamycins by the synthesis of compounds with the structures **2**. We first planned the stereoselective synthesis of a model

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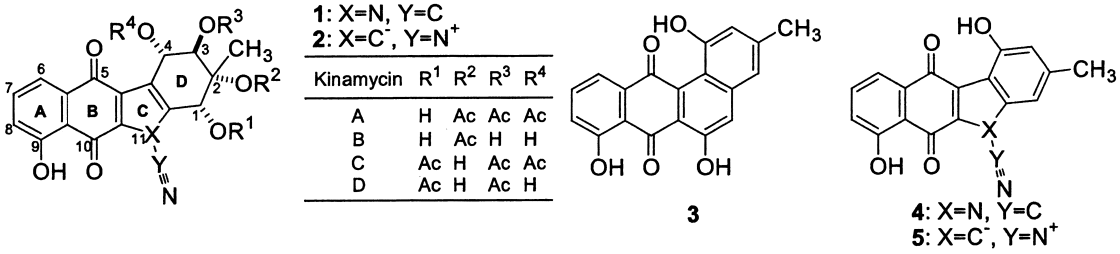
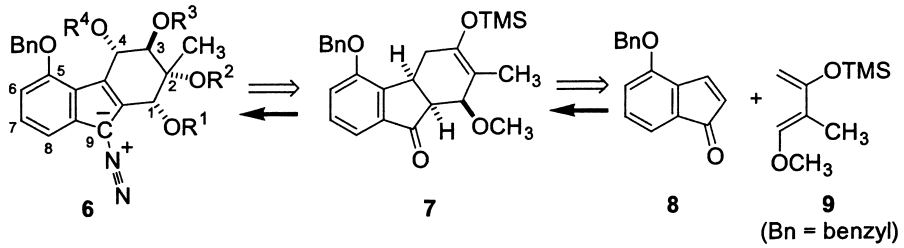


Figure 1.

compound **6** as shown in Scheme 1, in which a Diels–Alder reaction between an indenone **8** and a Danishefsky-type diene **9** was involved as a key step for the elaboration of a highly oxygenated cyclohexene ring.[8] In this paper, we report the first successful construction of a 3,4,5,6-tetra-oxygenated cyclohexene ring with a correct relative configuration (*cis*, *trans*, *trans* for hydroxy groups) in a kinamycin skeleton.



Scheme 1.

Diels–Alder reaction of **8**[9] and **9**[10] by refluxing in benzene smoothly afforded *endo* adduct **7**.[11] Desilylation of **7** under acidic conditions gave enone **10**,[12] a doubly activated position at C(9a) which was found to be easily oxygenated by molecular oxygen (O_2). Thus, treatment of **10** in DMSO under O_2 atmosphere in the presence of a catalytic amount of potassium fluoride[13] afforded γ-hydroxyenone **11**[14] in 63% yield from **8**. Hydroxyenone **11** was converted to the corresponding silyl dienol ether **12**, which was treated with OsO_4–NMO system followed by acidic work-up to afford a 5:1 mixture of 1,3-diols **13a** and **13b**. The mixture was subjected to

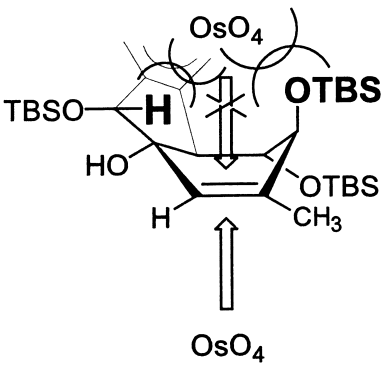


Figure 2. Direction of dihydroxylation with OsO_4 in the possible boat-like conformation of **15**

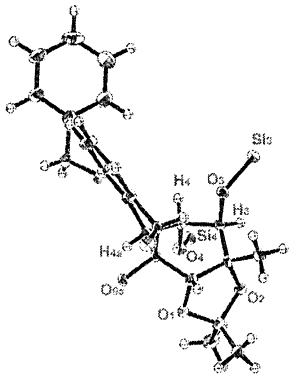
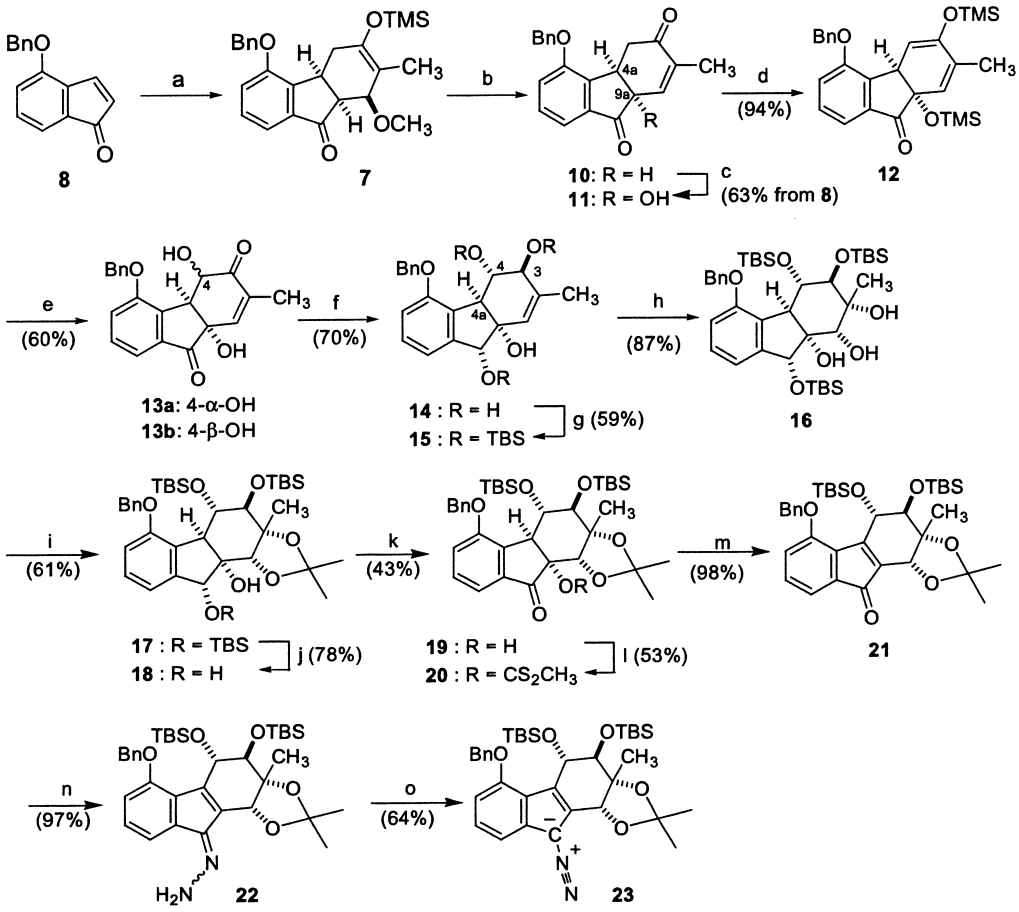


Figure 3. X-Ray structure of **18**. Alkyl groups on TBS were omitted for clarity



Scheme 2. (a) **9**, benzene, reflux, 2 h; (b) CSA, CH_2Cl_2, 0°C, 15 min; (c) O_2, KF (0.1 equiv.), DMSO, rt, 3 h; (d) TMSOTf, Et_3N, CH_2Cl_2, 0°C, 15 min; (e) (i) OsO_4 (0.05 equiv.), NMO, THF–H_2O (20:1), 0°C, 1 h, then rt, 24 h; (ii) 10% HCl; (f) DIBAL-H, THF, –78°C, 30 min, then recrystallization; (g) TBSCl, Et_3N, DMF, 50°C, 2.5 h; (h) OsO_4 (1 equiv.), pyridine, rt, 1 day; (i) 2,2-dimethoxypropane, acetone (5:1), TsOH·H_2O, 60°C, 19 h; (j) TBAF, THF, 0°C, 30 min; (k) PDC, CH_2Cl_2, rt, 24 h; (l) NaH, THF, rt, 1 h, then CS_2, rt, 1 h, then CH_3I, rt, 1 h; (m) 300°C, 20 mmHg (Kugelrohr), 15 min; (n) NH_2NH_2·H_2O, EtOH, reflux, 2 h; (o) Ag_2O, KOH (cat.), Et_2O, rt, 3 h

reduction with 4.5 equiv. of DIBAL-H in THF at –78°C followed by recrystallization from ethanol to give tetraol **14** with a correct stereochemical relationship[15] at C(3) and C(4). Protection of tetraol **14** with TBSCl gave tri-TBS ether **15**. The application of Kishi's prediction for the direction of dihydroxylation in allylic alcohol functions to **15** suggested the reaction from β-face.[16] However, no coupling between 3-H and 4-H and a small coupling constant ($J = 3.4$ Hz) between 4-H and 4a-H of **15** indicated a diaxial orientation of the OTBS groups at C(3) and C(4) due to the steric repulsion. In this situation, the concave face in **15** would be severely shielded by axial C(3)-OTBS group and C(9)-H in the possible boat-like conformation (Fig. 2). Thus, treatment of tri-TBS ether **15** in pyridine with a stoichiometric amount[17] of OsO_4 gave triol **16** with a desired configuration.[18]

Selective ketalization of triol **16** followed by desilylation with an equimolar amount of TBAF afforded diol **18** as only one isomer. The structure of **18** was determined by X-ray crystallography (Fig. 3). Oxidation of **18** with PDC gave α-hydroxyketone **19**, which was converted to the corresponding xanthate **20**. Pyrolysis of **20** under vacuum gave enone **21**. **21** was treated with hydrazine hydrate in ethanol to afford hydrazone **22** as a ca. 1:1 mixture of (*E*)- and (*Z*)-isomers. The mixture was dehydrogenated with Ag_2O in the presence of a catalytic amount of KOH to give a desired 9-diazotetrahydrofluorene **23** (Scheme 2). The absorption at 2067 cm^{-1} in the IR spectrum of **23** is in the range for those of the typical diazo compounds.[19]

In summary, we have succeeded in the elaboration of a highly oxygenated D-ring with correct stereochemistries for the kinamycin skeleton. Currently our efforts continue to improve ineffective steps and to complete the enantioselective total synthesis of kinamycins.

Acknowledgements

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18. The relative configration of **16** was determined by the X-ray crystallography.
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