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First Total Syntheses of Tetracenomycins C and X

Shogo Sato, Keiichiro Sakata, Yoshimitsu Hashimoto, Hiroshi Takikawa, and Keisuke Suzuki*

In memory of the late Professor Osamu Yonemitsu

Abstract: The first total syntheses of tetracenomycins C and X have been achieved, featuring 1) preparation of a hexasubstituted naphthonitrile oxide by successive benzyne cycloadditions and an oxidative ring-opening reaction; 2) a novel *ortho*-quinone mono-acetal as the A-ring unit; 3) construction of three contiguous stereogenic centers by an asymmetric benzoin cyclization, an isoxazole oxidation, and a stereoselective reduction.

We report the first total syntheses of stereogenic members of the tetracenomycin (TCM)-class antibiotics: TCMs C (**1**) and X (**2**), isolated as *Actinomycetes* metabolites, which exhibit broad activity against Gram-positive bacteria and cytotoxic activity against L1210 leukemia cells (Figure 1).[1] Their structures feature a densely oxygenated tetracycle with a characteristic AB-ring system bearing three contiguous stereogenic centers.[2] Biosynthetic studies by Hutchinson[3] revealed that the three stereogenic centers in the A-ring emerge from an oxygenase-mediated threefold hydroxylation of a fully-aromatized congener, TCM A2 (**3**), providing a general model for the biogenesis of this class of type-II polyketide metabolites.

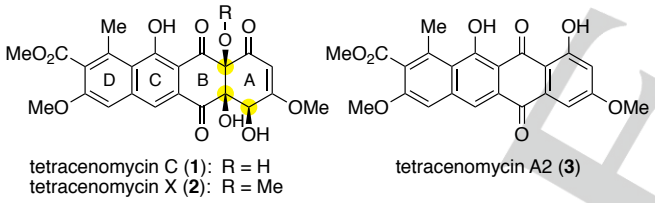


Figure 1. Structures of tetracenomycins C (**1**), X (**2**) and A2 (**3**).

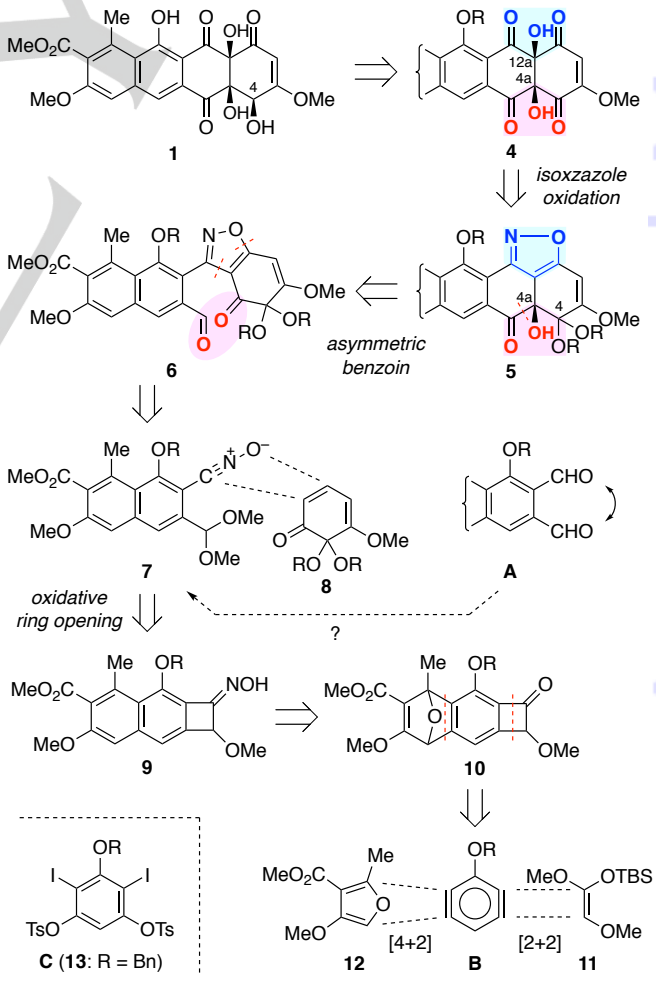
The important biological activities as well as the uniquely complex molecular architecture of TCMs have attracted considerable attention of synthetic community. However, despite more than 30 years have passed since the initial isolation report, the fully-aromatized congeners such as **3** have been the only members that were successfully synthesized.[4] The total syntheses of the stereogenic members had remained unachieved, which may have been due to formidable challenges that are posed by the stereochemical and functional complexity.

We identified three synthetic challenges, 1) the potential chemical instability of synthetic intermediates due to dehydrative aromatization, 2) the regiocontrolled installation of substituents on the tetracyclic core, and 3) the stereocontrolled construction of the angular *cis*-diol.

Herein, we describe the first total syntheses of **1** and **2** through an isoxazole-based polyketide assembling strategy,[5] including a two-step protocol for an isoxazole oxidation to construct the characteristic tetracyclic core with the angular *cis*-diol moiety.[6]

Our retrosynthetic analysis is shown in Scheme 1. The C4-alcohol is retrosynthetically oxidized to ketone **4**, aiming for a regio- and stereoselective hydride reduction at the final stage. The AB-ring system in **4** has a functional symmetry by the presence of two common 2-hydroxy-1,3-diketo structures (marked in blue and pink). We assumed that the upper functional array could be generated by a hydroxylation of isoxazole **5**,[6] while the lower one could be constructed by an asymmetric benzoin cyclization of ketoaldehyde **6**.[7]

Further disconnection of isoxazole **6** by assuming 1,3-dipolar



Scheme 1. Retrosynthetic analysis.

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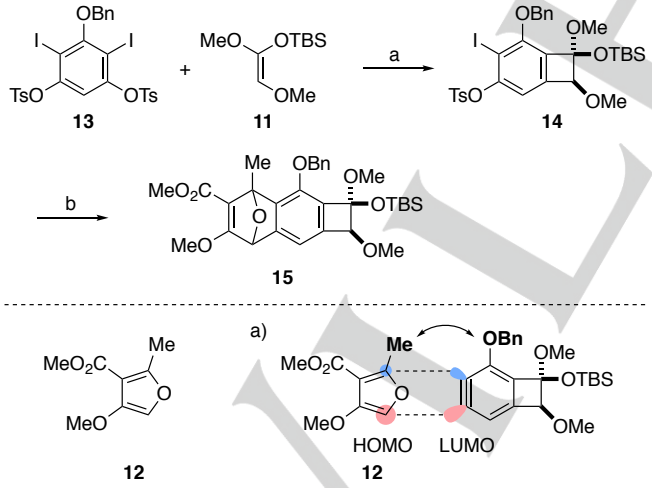
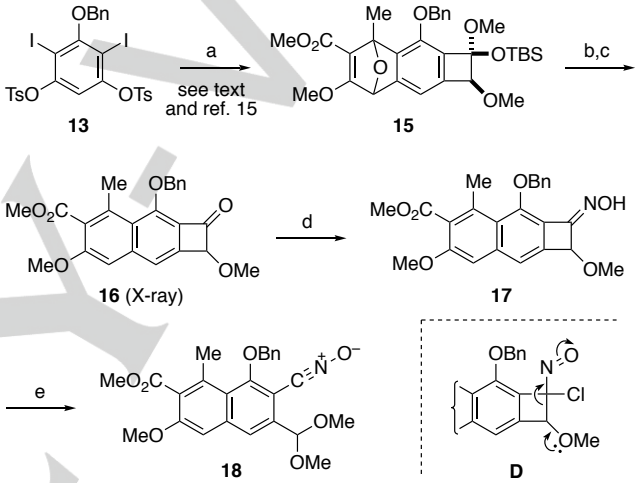
cycloaddition and dehydrogenation suggested naphthonitrile oxide **7** and *ortho*-quinone mono-acetal **8** as precursors.[8] Concerning the preparation of nitrile oxide **7** having six different substituents on its naphthalene core, conventional retrosynthetic analysis would suggest dialdehyde **A**, in which two formyl groups need to be discriminated as respective progenitors to the nitrile oxide and the acetal moiety in **7**. To overcome this issue, we recently developed a viable approach via oxidative ring opening of cyclobutenone oximes,[9] which allowed us to set oxime **9** as a precursor. Further disconnection of **9**, via the key tricycle **10**, suggested a three-component assembly by exploiting dual cycloadditions of 1,4-benzdiyne equivalent **B**.[10] Two relevant benzyne species would be sequentially generated from bis(tosyloxy)diiodobenzene **C**, reacting with two different arynophiles: [2+2] cycloaddition[11] with ketene silyl acetal (KSA) **11** and [4+2] cycloaddition with trisubstituted furan **12**.[12] Based on this analysis, we started the synthetic venture, and its successful implementation is described in the following.

The synthesis started with the generation of a benzyne species from bis-tosylate **13** (*n*-BuLi, THF, –95 °C, 10 min), which underwent the regioselective [2+2] cycloaddition to premixed KSA **11** (–95 → –20 °C, 1 h), giving benzocyclobutene **14** in 73% yield (Scheme 2).[13] The next step was the [4+2] cycloaddition of iodo-tosylate **14** with furan **12**[12] (*n*-BuLi, THF, –78 °C, 4 h), which gave two products. Pleasingly, careful structural analysis revealed these products to be stereoisomeric bis-cycloadducts **15** (d.r. = 1:1) due to the lack of facial selectivity relative to the stereogenic centers in **14**, but both were composed of single regioisomers as later proven by X-ray diffraction analysis (see **16**, Scheme 3). This rigorous regioselectivity could be rationalized by the primary orbital interaction as shown in Scheme 2a, which is notable in view of the potential conflict due to steric clash.[14]



Scheme 2. Dual benzyne cycloadditions. a) **11** (1.1 equiv), *n*-BuLi (1.1 equiv), THF, –95 → –20 °C, 1 h, (73%); b) **12** (1.5 equiv), *n*-BuLi (1.25 equiv), THF, –78 °C, 4 h (56%). Bn = benzyl, Ts = *p*-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl.

Furthermore, we established a one-pot protocol to perform the two successive benzyne cycloadditions (Scheme 3),[15] giving the bis-cycloadduct **15** in 44% yield, slightly higher than the stepwise protocol (vide supra, 41% yield in 2 steps). Bis-cycloadduct **15** was subjected to reductive aromatization ($TiCl_4$, Zn, THF, RT, 1 h)[16] followed by hydrolysis of the silyl acetal (aq. HF, MeCN, 0 °C, 1 h), giving benzocyclobutenone **16** in 78% yield. At this stage, the structure was unambiguously re-confirmed by X-ray diffraction analysis.[17] Ketone **16** was then converted to oxime **17** ($NH_2OH{\cdot}HCl$, pyridine, MeOH, 60 °C, 18 h) in 88% yield as a single isomer, whose *E*/*Z* configuration was not assigned. Pleasingly, the key oxidative ring opening[9] of oxime **17** proceeded nicely, via chloronitroso compound **D**, by treatment with NCS (2.4 equiv.) and Et_3N (2.4 equiv.) in a solvent mixture [MeOH, CH_2Cl_2 (v/v = 2/1), 0 °C, 1 h], giving naphthonitrile oxide **18** as a white solid in 73% yield.[18]



Scheme 3. Synthesis of naphthonitrile oxide **18**. a) **11** (1.1 equiv), *n*-BuLi, THF, –95 → –20 °C, 2 h, then **12** (1.5 equiv), *n*-BuLi, –78 °C, 20 min (44 %); b) $TiCl_4$, Zn, THF, RT, 1 h; c) aq. HF, MeCN, 0 °C, 1 h (78%, 2 steps); d) $NH_2OH{\cdot}HCl$, pyridine, MeOH, 60 °C, 18 h (88%); e) NCS, Et_3N, MeOH, CH_2Cl_2, 0 °C, 1 h (73%). NCS = *N*-chlorosuccinimide.

Having the requisite naphthonitrile oxide **18** in hand, the construction of the tetracyclic skeleton was examined (Scheme 4). Upon reaction of nitrile oxide **18** with the known *ortho*-quinone mono-acetal **19**[19] (PhCl, RT, 60 h), regioselective 1,3-dipolar cycloaddition proceeded smoothly to give isoxazoline **20** as a single product in 79% yield. After dehydrogenation of **20** (NiO_2, CH_2Cl_2, 0 °C, 30 min),[20] chemoselective hydrolysis of the benzylic acetal under acidic conditions (2 M H_2SO_4, THF, RT, 3 h) gave ketoaldehyde **21** in 95% yield, ready for the key benzoin cyclization.

The initial attempt at the benzoin cyclization was treatment of ketoaldehyde **21** with a combination of achiral triazolium salt **23a**[21] (30 mol%) and Et_3N (30 mol%). Although the desired α-ketol **22** was obtained, the yield was moderate (46%), and a considerable amount of ketoaldehyde **21** was recovered (20%). In spite of extensive investigations, we were not able to find suitable conditions to drive this reaction to full conversion.

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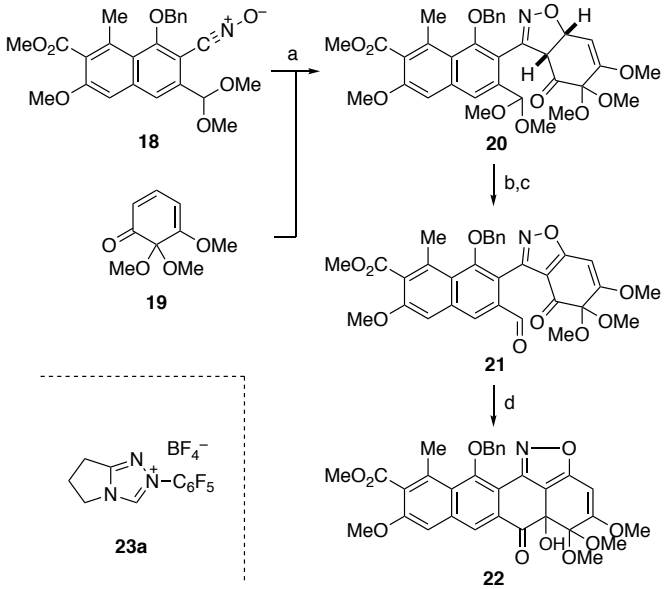
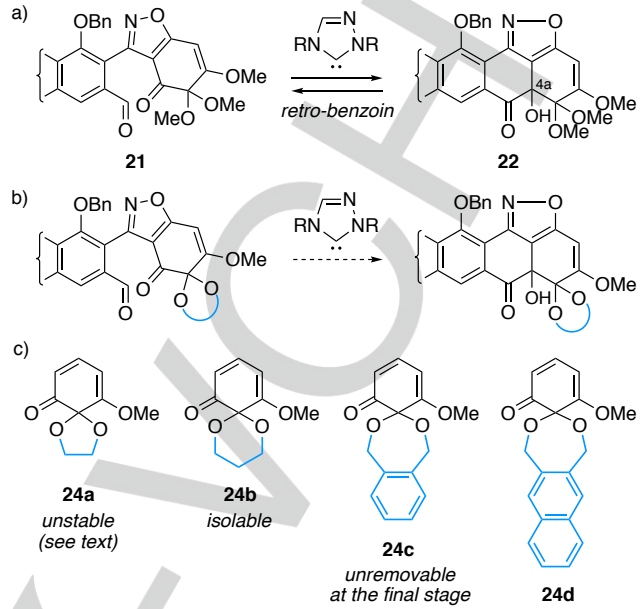


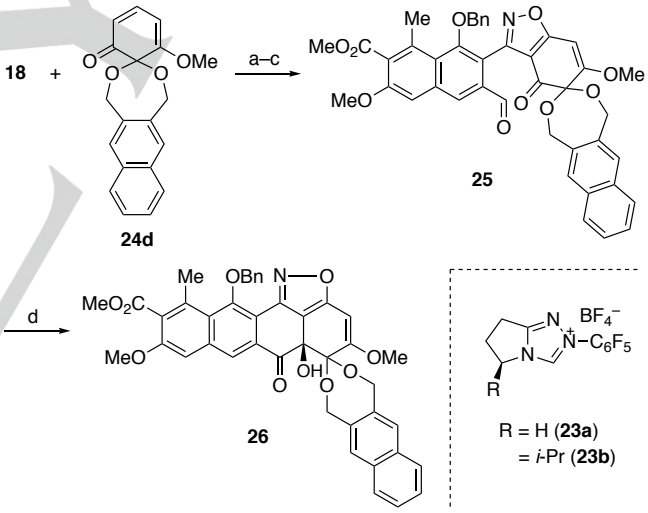
Scheme 4. Synthesis of α-ketol **22**. a) **19** (1.8 equiv), PhCl, RT, 60 h (79%); b) NiO_2, CH_2Cl_2, 0 °C, 30 min (82%); c) 2 M H_2SO_4, THF, RT, 3 h (95%); d) **23a** (30 mol%), Et_3N (30 mol%), THF, RT, 3 h [46% (20% recovery of **21**)].

Through the trials and errors, we noticed the presence of a retro-benzoin reaction as an origin of the problem (Scheme 5a),[22] and ascribed the unfavorable equilibrium to the high steric congestion of the α-ketol product **22** around its C4a angular position. We came up with the idea of lowering the steric demand by replacing the dimethyl acetal with a cyclic acetal (Scheme 5b),[23] and thus prepared four *ortho*-quinone mono-acetals **24a**–**d** with different cyclic acetal moieties (Scheme 5c). Extensive experimentation concluded that only **24d**[24] gave us the opportunity to complete the total synthesis as will be discussed later. Beforehand, it would be appropriate briefly to note the negative aspects of the other three acetals **24a**–**c**. First, ethylene acetal **24a** was unstable itself, easily undergoing dimerization.[25] By contrast, propylene acetal **24b** was stable enough for isolation, suggesting that cyclic acetals having six-membered ring or larger would be suitable for practical use. *ortho*-Xylylene acetal **24c** attracted our attention, which we hoped to be removable by acidic hydrolysis or hydrogenolysis.[26] Although not detailed due to space limitations, *ortho*-quinone mono-acetal **24c** turned out to be indeed a great substrate, allowing the transformations until the last synthetic intermediate immediately before the target **1**. Unfortunately, all attempts at the final deprotection failed.

However, we now pleasingly report that 2,3-dimethylnaphthalene-α,α'-diyl (DMN) acetal **24d** worked nicely for all steps, including the final oxidative deprotection,[27] enabling the total synthesis as follows. Scheme 6 shows the synthesis of α-ketol **26** having the DMN acetal moiety. Ketoaldehyde **25**, the direct precursor of **26**, was prepared by using the same protocol as above (vide supra, **18**+**19** → **20** → **21**): Reaction of DMN-acetal **24d**[28] (1.8 equiv) with nitrile oxide **18** (PhCl, 50 °C, 3.5 h) afforded the corresponding isoxazoline in 76% yield. Dehydrogenation (NiO_2, CH_2Cl_2, 0 °C, 1 h) and hydrolysis (2 M H_2SO_4, THF, RT, 3 h) gave ketoaldehyde **25** in 80% yield in 2 steps, ready for the crucial benzoin cyclization.



Scheme 5. Problem and solution for the benzoin cyclization.



Scheme 6. Synthesis of α-ketol **26**. a) **18** + **24d** (1.8 equiv), PhCl, 50 °C, 3.5 h (76%); b) NiO_2, CH_2Cl_2, 0 °C, 1 h (82%); c) 2 M H_2SO_4, THF, RT, 3 h (97%); d) **23a** or **23b** (15 mol%), Et_3N (15 mol%), THF, RT, 3 h (89% with **23a**; 87%, >99% ee with **23b**).

Pleasingly, upon treatment with achiral triazolium salt **23a** (15 mol%) and Et_3N (15 mol%) (THF, RT, 3 h), the benzoin cyclization of **25** proceeded smoothly to completion, affording α-ketol **26** in 89% yield. Thus, the use of a cyclic acetal realized full conversion of the benzoin cyclization. Furthermore, screening of chiral triazolium salts identified Rovis' triazolium salt **23b**[29] as the best catalyst precursor, allowing the enantioselective cyclization of **25** to give α-ketol **26** [(*R*)-

configuration][30] in high yield and perfect enantioselectivity (87%, >99% ee).[31]

Scheme 7 shows the successful route to the target **1** from α-ketol **26**, which called for another subtle selection of the protecting group for the C4a-OH.[32] Among various protecting groups tested, the [D_7]benzyl group[33] (Bn*) provided us with the desired stability for the further transformations as discussed below. The *tert*-hydroxy group in **26** was protected by a Bn* group (Bn*Br, NaH, DMF, –20 → 0 °C, 1 h). *N*-Methylation ($Me_3O^+BF_4^-$, MS4A, CH_2Cl_2, RT, 14 h) followed by precipitation (Et_2O/EtOAc = 9/1) gave isoxazolium salt **27** in excellent yield. Upon treatment of **27** with NaOCl (acetone, –40 °C, 10 min) under carefully controlled conditions (pH 8.9),[34] the hydroxylation proceeded smoothly to give the desired alcohol **29a** in 66% yield as a single diastereomer.

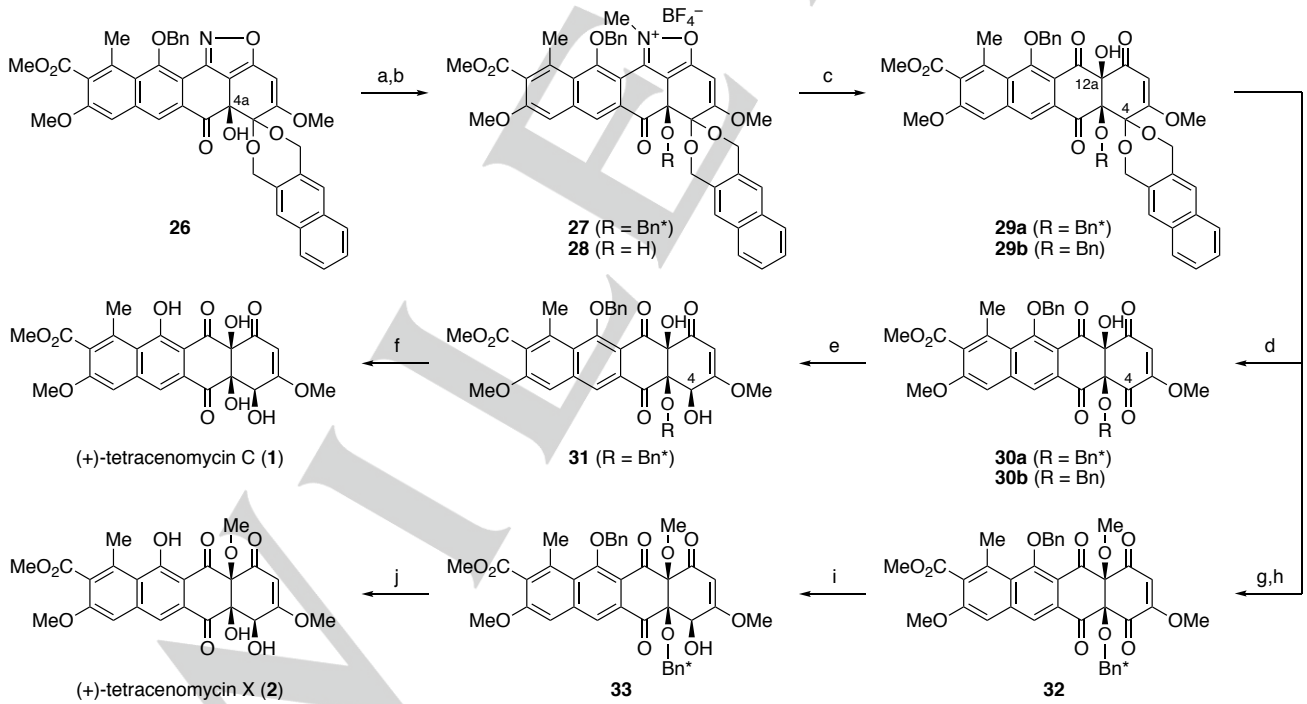
Liberation of the C4 carbonyl group proved to be a challenge, as it failed either by acid hydrolysis or by hydrogenolysis. Pleasingly, an oxidative protocol proved effective, and treatment of **29a** with DDQ (2,6-di-*tert*-butylpyridine, CH_2Cl_2, 80 °C, 6 h) gave ketone **30a** in 78% yield. At this step, the Bn* protecting group played a key role; serious degradation was observed for the alcohol **29b** having a non-deuterated benzyl group under the same conditions, primarily due to the undesired oxidation at the benzylic position.[35] We chose the Bn*-protecting group in hope of its increased robustness toward oxidation by kinetic isotope effect,[36] which indeed gave a positive result (vide supra).

With tetraketone **30a** in hand, the remaining tasks toward the total synthesis were: 1) the reduction of the C4 carbonyl group, and 2) the deprotection of two benzyl groups. Since ketone **30a** was base-labile, we decided to employ sodium cyanoborohydride as a reductant under acidic conditions. Pleasingly, the chemo- and stereoselective reduction was achieved under carefully optimized conditions with two key requirements: 1) the use of CH_2Cl_2 as a solvent, and 2) the use of minimal amounts of acid. Treatment of ketone **30a** with $NaBH_3CN$ in CH_2Cl_2 and AcOH (v/v = 30:1, 0.02 M, 0 °C, 2 h) afforded β-alcohol **31** as a major product (78% yield, β:α = 4.2:1). The minor C4-epimer was separable by column chromatography (diol-modified SiO_2, hexane/EtOAc = 7/3→1/1), and in turn recycled by oxidation to ketone **30a**.[37]

The final step was hydrogenolytic removal of two benzyl groups using $PdCl_2$ (H_2, AcOH, H_2O, MeOH, RT, 1 h), and the purification by column chromatography (diol-modified SiO_2, hexane/EtOAc = 1/1→1/4) gave the target **1** in 70% yield, which showed physical data (^{1}H-, ^{13}C NMR, IR, HRMS) identical in all respects to those reported for the natural product, including the optical rotation in sign and magnitude, $[\alpha]_D^{24}$ +22.2 (*c* 1.00, 1,4-dioxane), *lit.* $[\alpha]_D^{24}$ +22 (*c* 1, 1,4-dioxane)].[1]

Furthermore, after methylation of the C12a alcohol in **29a** (MeI, NaH), the same sequence of final conversion stated above gave tetracenomycin X (**2**), which also exhibited physical data consistent with the reported data for the natural product $[\alpha]_D^{20}$ +105 (*c* 0.290, MeOH), *lit.* $[\alpha]_D^{20}$ +108.4 (*c* 0.66, MeOH)].[38]

In summary, the first asymmetric total syntheses of tetracenomycins C (**1**) and X (**2**) have been achieved. The synthetic route is efficient, and thus allows the synthesis of various congeners with potential biological activities. Further work along these lines is in progress.



Scheme 7. Endgame. a) Bn*Br, NaH, DMF, –20 → 0 °C, 1 h (94%); b) $Me_3O^+BF_4^-$, MS4A, CH_2Cl_2, RT, 14 h (97%); c) aq. NaOCl (pH 8.9), acetone, –40 °C, 10 min (66%); d) DDQ, 2,6-di-*tert*-butylpyridine, 1,2-dichloroethane, 80 °C, 6 h (**30a**: 78% from **29a**, **30b:** 35% from **29b**); e) $NaBH_3CN$, AcOH, CH_2Cl_2, 0 °C, 2 h (78%, d.r. 4.2:1); f) H_2 (balloon), $PdCl_2$, AcOH, H_2O, MeOH, RT, 1 h (70%); g) MeI, NaH, DMF, 0 °C, 30 min (90%); h) DDQ, 2,6-di-*tert*-butylpyridine, 1,2-dichloroethane, 80 °C, 4.5 h (75%); i) $NaBH_3CN$, AcOH, CH_2Cl_2, 0 °C, 3 h (83%, d.r. 4.9:1); j) H_2 (balloon), $PdCl_2$, AcOH, H_2O, MeOH, RT, 3 h (76%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Bn* = [D_7]benzyl.

Acknowledgments

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Keywords: antibiotics • total synthesis • benzyne • nitrile oxide • isoxazole

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[12] Facile preparation of trisubstituted furans, including **12**, and their regioselective [4+2] cycloaddition with α-alkoxybenzyne have been recently reported. See S. Sato, T. Kawada, H. Takikawa, K. Suzuki, *Synlett* **2017**, DOI: 10.1055/s-0036-1590825.

[13] A related bis-sulfonate, in which one of the sulfonate is a triflate (ref. 10a), was less satisfactory. We were pleased to find that bis-tosylate **13**, easier to prepare, worked nicely by choosing a suitable set of conditions. Particularly, careful control of the temperature was crucial.

[14] For previous model studies, see ref. 12.

[15] Experimental procedure: Bis-tosylate **13** was treated with *n*-BuLi (1.1 equiv) in the presence of KSA **11** (1.1 equiv) (THF, –95 → –20 °C, 2 h). TLC-control showed that the starting material was consumed, and mono-cycloadduct **14** (R_f 0.73, hexane/EtOAc = 1/1) was formed. Furan **12** (1.5 equiv) was added to the reaction mixture, which was chilled to –78 °C, and *n*-BuLi (1.25 equiv) was slowly added over 5 min. Further stirring for 20 min gave bis-cycloadducts **15** as a mixture of two diastereomers (1:1, R_f 0.67, 0.60, hexane/EtOAc = 1/1) in 44% combined yield.

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[17] CCDC 1543805 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] Nitrile oxide **18** could be stored at –18 °C for at least one month.

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[31] The enantiomeric purity of α-ketol (*R*)-**26** was assessed by HPLC analysis using a chiral stationary phase, which allowed good separation of the racemic sample of **26**; see Supporting Information.

[32] Prior protection of C4a-OH was essential: reaction of the isoxazolium salt **28** with the C4a-OH unprotected failed, giving no hydroxylated product under the same conditions.

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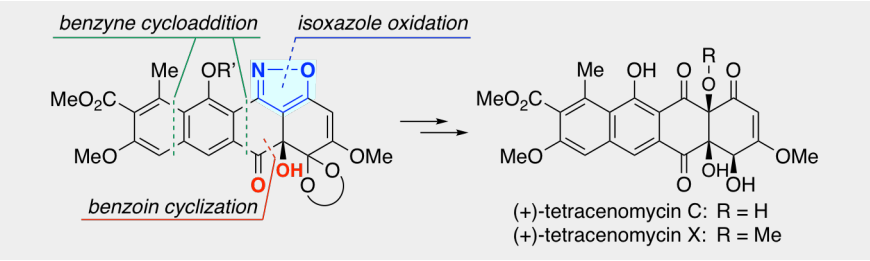

The first total syntheses of tetracenomycins C and X have been achieved, featuring 1) preparation of a hexasubstituted naphthonitrile oxide by successive benzyne cycloadditions and an oxidative ring-opening reaction; 2) a novel *ortho*-quinone mono-acetal as the A-ring unit; 3) construction of three contiguous stereogenic centers by an asymmetric benzoin cyclization, an isoxazole oxidation, and a stereoselective reduction.

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