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Total synthesis of BE-23254, a chlorinated angucycline antibiotic

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Abstract—The first synthesis of BE-23254, an unusual angucycline antibiotic, is reported. It involves regioselective condensation of naphthalenone **4** and chlorine-containing isobenzofuranone **16** as the key step.
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The angucycline antibiotics are a large group of naturally occurring quinone metabolites from microbial sources.[1,2] They exhibit a wide range of biological activities, which include antibiotic and antiviral activities, enzyme inhibitory effects, vincristine cytotoxicity potentiating activity and antigastrin activity. Although all the members share a benz[*a*]anthraquinone framework of decaketide origin, the structural diversity among the members is very broad. They occur in a large variety of oxidation states. The main differences are observed in the aromaticity of the A and B rings, in the location of the hydroxyl groups and the *O*-glycosidic linkages. BE-23254 (**1**), an antitumour agent was isolated from *Streptomyces* sp. A 23254.[3] It was reported to exhibit activity against the human colon cancer DLD-1 (IC_{50} 0.75 μg ml^{-1}). Structurally, it is unique amongst all presently known angucyclines and angucyclinones in that it bears a chlorine atom at C-9. The methyl group at C-3, which is present in almost all other angucyclines, is absent in BE-23254. Additionally, a carboxy group is present at C-2. These unusual structural features prompted us to undertake the total synthesis of this molecule.

Several strategies have been reported for the synthesis of this structurally diverse group of natural products.[4] These include Diels–Alder methodology, Michael-type cyclization, Hauser–Kraus annulation, Friedel–Crafts reaction, free radical annulation, [2+2+2] cycloaddition, nucleophilic addition, cyclobutenone rearrangement, benzyne cycloaddition and biomimetic polyketide condensation. We report herein the first total synthesis of BE-23254 (**1**) using the Hauser–Kraus annulation of a partially dearomatized naphthalene derivative.

Previously, we have reported that 4a-methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one can be regiospecifically annulated with benzoisofuranones to give 6-hydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-diones in excellent yields.[5a,b] This finding has been successfully applied to the total synthesis of brasiliquinones, in which the A-rings are non-aromatic.[5c] It was felt that such a strategy would also be very suitable for accessing BE-23254 and its analogues, in which the A-ring is aromatic. Accordingly, we planned to synthesize **1** via aromatization of **2**, obtainable by reaction of isobenzofuranone **3** with naphthalenone **4** (Scheme 1).

For the synthesis of **4**, commercially available 6-methoxytetralone **5** was chosen as the starting material. Following the literature[6] sequence, it was converted to tetrahydronaphthalene-2-carboxylic acid **6** in 43% overall yield (Scheme 2). Reaction of this product with HBr in acetic acid under standard conditions proceeded to give phenolic acid **7a**,[7] which was selectively protected[8] as methyl ester **7b**, upon treatment with DBU and iodomethane. The crucial dearomatization of **7b** to naphthalenone **4** was regioselectively performed in 65% yield by reaction with phenyliodonium diacetate (1.2 equiv) in methanol. The stereostructure of the compound **4** could not be ascertained by analysis of the coupling constants due to difficulty in assigning the signals.

We then focused our attention to the synthesis of CD synthon **3**. Since the phenolic ester **8**[9] was easily accessible, we briefly studied its direct chlorination with selected chlorinating agents to obtain chloro compound

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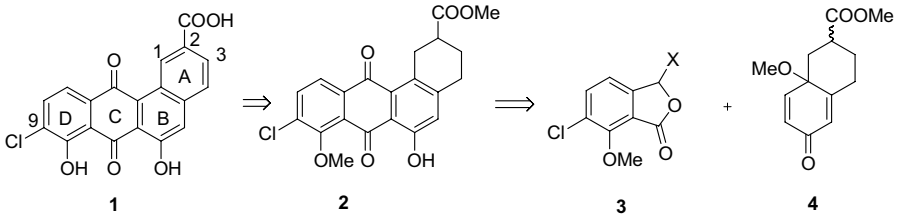
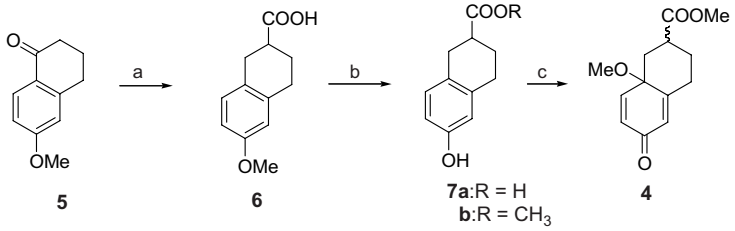


Scheme 1. Retrosynthesis of BE-23254 (**1**).



Scheme 2. Reagents and conditions: (a) (i) $NaBH_4$, MeOH, rt, 96%; (ii) $POCl_3$, DMF, 100 °C, 72%; (iii) Ag_2O, EtOH–H_2O, rt, 81%; (iv) H_2, 10% Pd–C, EtOH, rt, 91%; (b) (i) HBr, AcOH, reflux, 81%; (ii) DBU (2 equiv), CH_3CN, CH_3I (1 equiv), rt, 96%; (c) $PhI(OAc)_2$ (1.2 equiv), MeOH, 0 °C–rt, 65%.

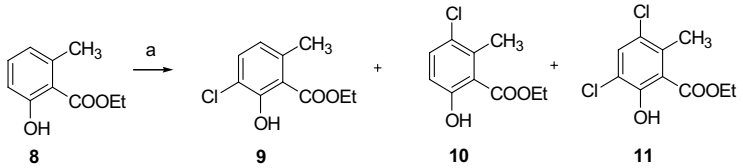
Table 1. Product distribution of chlorination of phenol **8**

Reagents and conditions	% Yield of **9**	% Yield of **10**	% Yield of **11**
Cl_2 (1.2 equiv), AcOH, rt[a]	—	74	—
SO_2Cl_2 (1.5 equiv), 100 °C, 3 h	—	—	65
Cl_2 (1.2 equiv), AcOH, rt[b]	—	47	21
NCS (1.1 equiv), CCl_4, reflux, 4–5 h	11	53	—
NaOCl (1.1 equiv), AcOH, reflux, 4–5 h	Trace	15	49
NCS (1.1 equiv), AcOH, reflux, 4–5 h	Trace	35	—

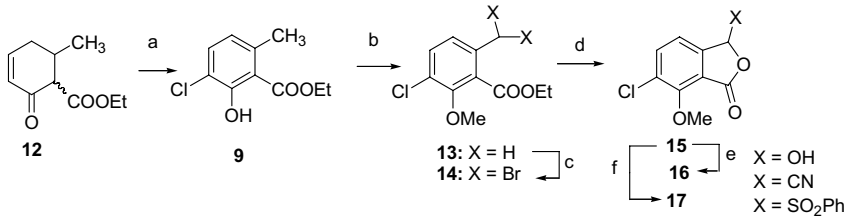
[a] A Cl_2/AcOH solution was added dropwise to the solution of phenol **8** in AcOH.
[b] Phenol **8** was added to a solution of Cl_2 in AcOH.

9. It may be noted that methods for selective chlorination of substituted phenols are rare in the literature.[10] The phenolic ester **8** was prepared in two steps from ethyl acetoacetate and crotonaldehyde according to the published procedure,[9] and then subjected to chlorination under different conditions. The results of the chlorinations are presented in Table 1. As anticipated, the chlorination was not regioselective. The majority of the experiments failed to provide the desired chloro derivative **9**. Determination of the structures of the monochlorinated products **9** and **10** was based on NOE experiments (Scheme 3).

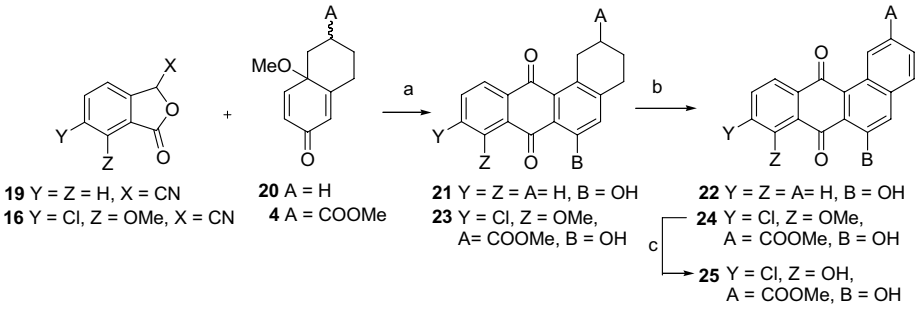
Finally, the problem of preparing the monochlorophenol **9** was solved via chlorination of cyclohexenone **12**,[11] the immediate precursor of phenol **8** (Scheme 4). Treatment of **12** with 2 equiv of SO_2Cl_2 in CCl_4 followed by treatment with DBU (3 equiv) at room temperature afforded, after work-up, phenol ester **9** in 41% yield. Subsequent conversion of **9** into **14** was achieved in two steps. Protection of the phenolic OH with dimethyl sulfate in the presence of K_2CO_3 gave **13**, which was subjected to benzylic bromination with NBS (2 equiv) to produce dibromo derivative **14**. This was then hydrolyzed with a refluxing mixture of AcOH–HCl–water to give phthalaldehydic acid **15**. Two key synthons **16** and **17** were, respectively, prepared according to the general procedures developed for the preparation of cyanophthalides and phenylsulfonylphthalides. Reaction of phthaladehydic acid with KCN in the presence of concd HCl furnished the cyanophthalide **16** in 83% yield.[12] Its structure was established by analysis of the spectral data. Similarly, the corresponding phthalide sulfone **17** was prepared in 70% yield according to our



Scheme 3. Reagents and conditions: (a) see Table 1.



Scheme 4. Reagents and conditions: (a) (i) SO_2Cl_2 (2 equiv), CCl_4, 78 °C; (ii) DBU (3 equiv), C_6H_6, rt, 41%; (b) K_2CO_3, Me_2SO_4, acetone, 55–56 °C, 68%; (c) NBS (2 equiv), $(BzO)_2$, CCl_4, 78 °C, 67%; (d) AcOH–HCl–water, 100 °C, 72%; (e) KCN, HCl, 0 °C–rt, 83%; (f) $PhSO_2OH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 70%.



Scheme 5. Reagents and conditions: (a) LiO^{t}Bu, THF, −60 to 0 °C, 71%; (b) DDQ, benzene, reflux, 49%; (c) $AlCl_3$, CH_2Cl_2, rt, 78%.

procedure by reacting the acid **15**[13] with phenylsulfinic acid in the presence of $BF_3{\cdot}$etherate.[14]

Before examining the proposed annulation (Scheme 1), we studied the aromatization of the model compound **21**, which was prepared from **19** and **20** by our published procedure.[5a] Treatment of **21** with DDQ (6 equiv) in refluxing benzene effected aromatization of the A ring to give compound **22**[15] in 67% yield. NMR analysis of an interrupted reaction mixture showed the formation of an inseparable mixture of didehydro intermediates along with the desired product **22** (Scheme 5).

Since the reactivity of the naphthalenone **4** towards phthalide annulation was unknown, we attempted to annulate it with phthalide sulfone **17**.[5a] Reaction of phthalide sulfone **17** with naphthalenone **4** in the presence of lithium *tert*-butoxide from −60 to 0 °C, followed by stirring at room temperature and routine work-up did not yield the expected annulated product **23**. Naphthalenone **4** could be recovered from the reaction in a substantial yield, whereas phthalide sulfone **17** was destroyed during the reaction. However, condensation of cyanophthalide **16** with **4** in the presence of LiO^{t}Bu at −60 °C provided tetrahydrobenz[*a*]anthraquinone **23** in 71% yield. Aromatization of the A-ring in **23** was effected with DDQ in refluxing benzene to provide **24** in 49% yield, which was primarily characterized by examination of ^{1}H NMR and mass spectral data.[16] Demethylation of compound **24** was effected by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature to provide **25** in 78% yield. Base (NaOH) catalyzed hydrolysis of **25** yielded the natural product **1** in 92% yield.[17]

In summary, we have completed the first regioselective total synthesis of BE-23254, an unusual angucycline antibiotic. In the process, we have introduced a new approach for the preparation of *ortho*-chlorinated phenols based on chlorinative aromatization of a cyclohexenone derivative. Further study on the synthesis of bromo and fluoro analogues of BE-23254 is in progress.

Acknowledgements

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16. ^{13}C NMR data could not be recorded due its poor solubility in common deuterated organic solvents.
17. The compounds gave satisfactory elemental analyses, EIMS and NMR data. Selected spectroscopic data: Compound **1**: Mp 324–326 °C; ^1H NMR (d_5-pyridine, 200 MHz): δ 10.9 (1H, s), 8.55 (1H, d, J = 8.3 Hz), 7.90–7.81 (4H, m); HRMS *m/z* (ESI): calcd for $C_{19}H_9O_6Cl$ (M^+-H): 367.0009; found: 367.0026. Compound **4**: Waxy solid; IR ν_{max} (KBr, cm^{-1}): 1735, 1667, 1636, 1441, 1305, 1207, 1085, 987, 891; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.64 (1H, d, J = 10.1 Hz), 6.63 (1H, dd, J = 1.7, 10.1 Hz), 6.21 (1H, d, J = 1.7 Hz), 3.65 (3H, s), 3.02 (3H, s), 2.53–2.20 (5H, m), 1.60–1.41 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 185.76, 174.65, 160.49, 149.79, 131.32, 127.09, 72.75, 51.82, 51.66, 40.55, 37.46, 31.04, 29.91. Compound **9**: Mp 55–56 °C; IR ν_{max} (KBr, cm^{-1}) 3442, 1663, 1424, 1256, 1205, 802; ^1H NMR ($CDCl_3$+CCl_4, 200 MHz): δ 11.97 (1H, s), 7.37 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 8.2 Hz), 4.45 (2H, q, J = 7.2 Hz), 2.52 (3H, s), 1.44 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.38, 158.15, 140.01, 133.96, 122.76, 119.88, 113.58, 62.15, 23.81, 14.08. Compound **16**: Mp 90–91 °C; IR ν_{max} (KBr, cm^{-1}) 1788, 1601, 1390, 1024, 768; ^1H NMR ($CDCl_3$+CCl_4, 200 MHz): δ 7.82 (1H, d, J = 8.1 Hz), 7.31 (1H, d, J = 8.1 Hz), 6.97 (1H, s), 4.21 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.80, 155.50, 141.62, 137.53, 130.26, 117.43, 116.61, 113.19, 64.56, 62.86; **MS** *m/z* (EI): 223 (M^+), 205, 194, 177, 167, 149. Compound **23**: Orange solid; mp 135–136 °C; IR ν_{max} (KBr, cm^{-1}): 3408, 1733, 1634, 1273, 1025, 763, 697; ^1H NMR ($CDCl_3$, 200 MHz): δ 13.00 (1H, s), 7.99 (1H, d, J = 8.3 Hz), 7.82 (1H, d, J = 8.3 Hz), 7.06 (1H, s), 4.01 (3H, s), 3.74 (3H, s), 3.61 (1H, dd, J = 5.6, 18.6 Hz), 3.31 (1H, dd, J = 10.1, 18.6 Hz), 2.94–2.89 (2H, m), 2.80–2.68 (1H, m), 2.21–2.12 (1H, m), 2.03–1.90 (1H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 187.79, 183.75, 175.37, 160.74, 156.07, 147.76, 136.53, 135.79, 135.24, 131.76, 129.87, 126.21, 124.52, 124.25, 116.39, 61.62, 51.92, 39.83,30.94, 29.89, 24.15; MS *m/z* (EI): 400 (M^+), 369, 340, 326, 322, 297, 284, 256, 236, 197. Compound **24**: Red solid; mp 234–235 °C; ν_{max} (KBr, cm^{-1}) 3426, 1725, 1644, 1570, 1459, 1314, 1265, 1222, 1019, 760; ^1H NMR ($CDCl_3$, 200 MHz): δ 12.42 (1H, s), 10.04 (1H, s), 8.12 (1H, d, J = 8.4 Hz), 8.08 (1H, d, J = 8.6 Hz), 7.86 (1H, d, J = 8.4 Hz), 7.75 (1H, d, J = 8.6 Hz). 7.68 (1H, s), 4.06 (3H, s), 4.01 (3H, s); HRMS *m/z* (ESI): calcd for $C_{21}H_{13}O_6Cl$ (M^++H): 397.0479; found: 397.0468. Compound **25**: Red solid; mp 273–274 °C; ^1H NMR ($CDCl_3$, 200 MHz): δ 12.34 (1H, s), 11.90 (1H, s), 10.15 (1H, s), 8.14 (1H, dd, J = 1.5, 8.7 Hz), 7.83 (2H, s), 7.76 (1H, d, J = 8.7 Hz), 7.71 (1H, s), 4.02 (3H, s); HRMS *m/z* (ESI): calcd for $C_{20}H_{11}O_6Cl$ (M^+-H): 381.0166; found: 381.0150.