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Stereoselective total syntheses of (±)-arthrinone and related natural compounds

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Abstract

The first total syntheses of (±)-arthrinone, (±)-1-dehydroxyarthrinone, and (±)-3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone, antifungal metabolites from the coprophilous fungus *Cercophora sordarioides*, were accomplished in a stereoselective manner. The ring systems of these metabolites, which were rare among natural products, were efficiently and diastereoselectively assembled using the [2,3]Wittig rearrangement and Diels–Alder reaction as the key steps.

Keywords: antifungal metabolites; oxyselenenylation; [2,3]Wittig rearrangement; Diels–Alder reaction.

Arthrinone (**1**) was originally isolated in 1994 as an antifungal metabolite from *Arthrinium* sp. FA 1744, and its relative stereostructure was confirmed by X-ray crystallographic analysis.[1a] In 1997 it was also isolated from coprophilous fungus *Cercophora sordarioides* along with three structurally related compounds:[1b] 1-dehydroxyarthrinone (**2**), 3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone (**3**), and cerdarin (**4**), some of which exhibited anti-*Candida* and antibacterial activity. Compounds **1**, **2**, and **3** have unique structural features, namely, the epoxynaphtho[2,3-*c*]furan ring system in a semiquinone form, which is rare among natural products. But to date, the absolute stereochemistries of them were not confirmed unambiguously. Only the absolute stereochemistry at C-4 of **2** was assigned by ^{1}H NMR analyses of the corresponding (*R*)- and (*S*)-2-phenylbutyric acid monoesters (Helmchen's method), while every other stereochemistry was proposed as shown in Fig. 1 by assuming the biosynthetic pathway of the resemblance between **1**, **2**, and **3**, and by considering NMR similarities. The absolute stereochemistry at C-3 of **4** was not elucidated, moreover, as for C-3a of **3**, even its relative stereochemistry remains undefined. Such a situation prompted us to undertake their asymmetric syntheses. In this paper, we report the stereoselective total syntheses of (±)-**1**, (±)-**2**, and (±)-**3** as the preliminary study toward their asymmetric syntheses.

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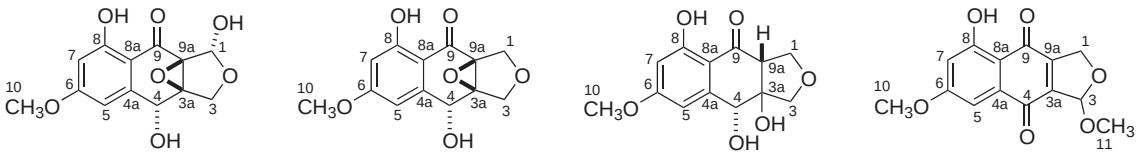
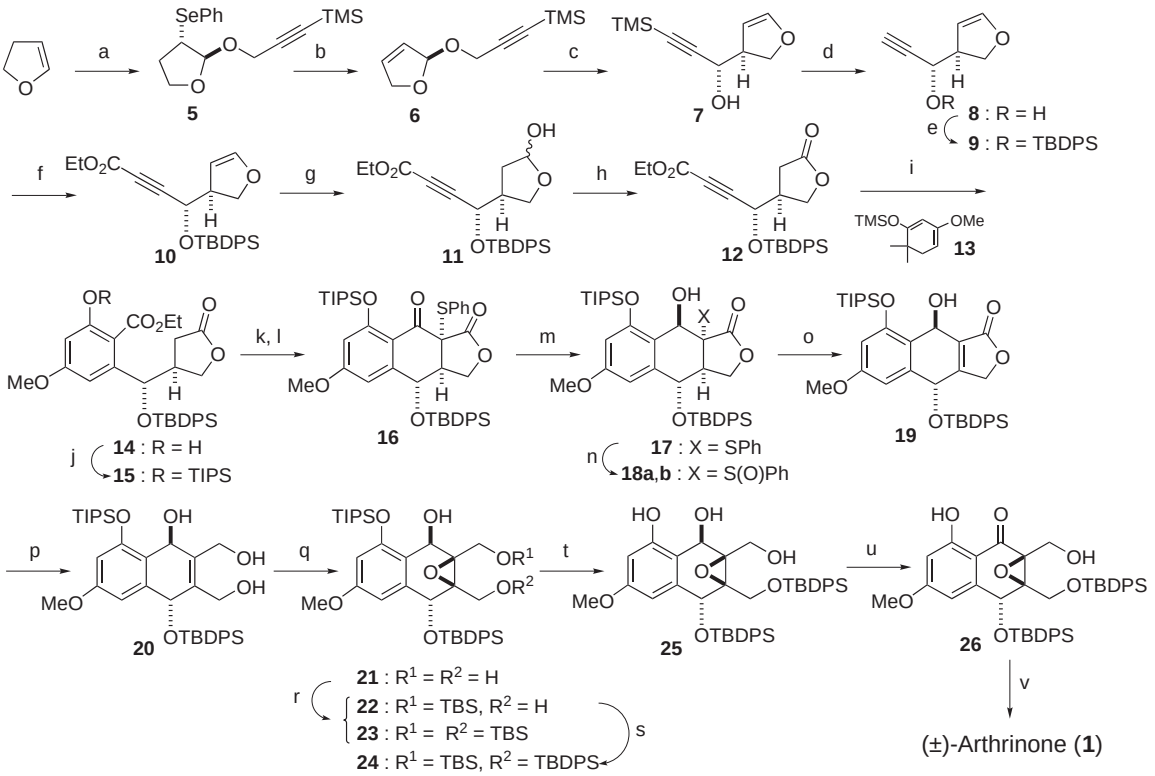
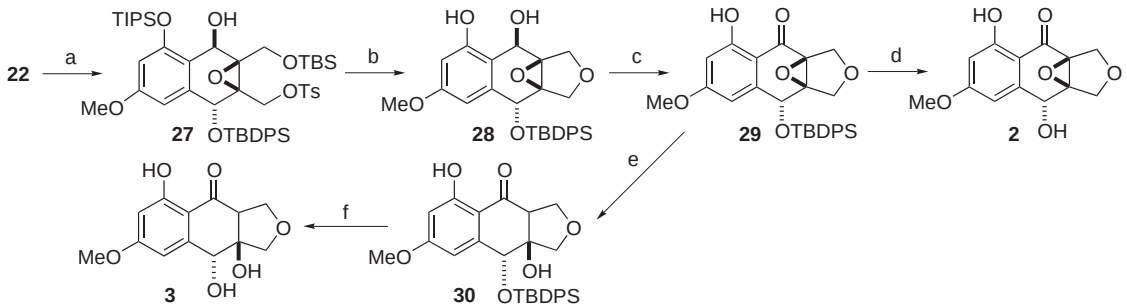


Figure 1.

Our syntheses are illustrated in Schemes 1 and 2. As the starting material we used commercially available 2,3-dihydrofuran, which was transformed to **6** by the oxyselenenylation–oxidative deselenenylation sequence. Compound **6** was diastereoselectively converted to alcohol **7** using the [2,3]Wittig rearrangement reported by Nakai and co-workers.[2,3]



Scheme 1. *Reagents and conditions*: (a) PhSeCl, CH_2Cl_2, −78°C; then 3-trimethylsilyl-2-propyn-1-ol, −78→−50°C, 94%; (b) 30% H_2O_2, $NaHCO_3$, AcOEt, THF, 0°C→rt, 86%; (c) *n*-BuLi, THF, −78°C, 95%; (d) TBAF, THF, 0°C→rt, 98%; (e) TBDPSCl, imidazole, DMF, rt, 85%; (f) *n*-BuLi, THF, −78°C; then $ClCO_2Et$, −78°C→rt, 96%; (g) AcOH, THF, H_2O, rt, 93%; (h) PCC, MS 4 Å, CH_2Cl_2, 0°C→rt, 95%; (i) **13**, 160°C; then THF, 5% HCl, rt, 81%; (j) TIPSCl, imidazole, DMF, rt, 100%; (k) NaHMDS, THF, −78°C; (l) NaH, THF, 0°C; then PhSCl, 87% from **15**; (m) $Zn(BH_4)_2$, CH_2Cl_2, 0°C, 83%; (n) *m*CPBA, CH_2Cl_2, 0°C, (**18a**: 81%, **18b**: 9%); (o) $P(OMe)_3$, toluene, reflux, 89% from **18a**, 76% from **18b**; (p) DIBAL-H, CH_2Cl_2, −78°C; then $NaBH_4$, MeOH, 0°C, 77%; (q) *m*CPBA, CH_2Cl_2, phosphate buffer (pH 7.9), 0°C→rt, 72%; (r) TBSOTf, pyridine, THF, −60°C, (**22**: 78%, **23**: 12%); (s) TBDPSCl, imidazole, DMF, rt, 91%; (t) 5% NaOH in EtOH, THF, rt, 61%; (u) MnO_2, acetone, rt, 91%; (v) cat. TPAP, NMO, MS 4 Å, CH_2Cl_2, rt; then TBAF, AcOH, THF, rt, 73%



Scheme 2. *Reagents and conditions*: (a) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 100%; (b) 5% NaOH in EtOH, THF, rt; then DMSO, H_2O, 90°C, 63%; (c) MnO_2, acetone, rt, 100%; (d) TBAF, AcOH, THF, rt, 74%; (e) NaTeH, EtOH, THF, 0°C, 77%; (f) TBAF, AcOH, THF, rt, 87%

We next set about constructing the aromatic ring by the Diels–Alder reaction. The first requirement was incorporating an ethoxycarbonyl group into the alkyne terminus. This group was presumed to activate the C–C triple bond as dienophile, and to be a source of C-9 in the target compounds. Thus **7** was converted to **10** in three straightforward steps. Direct oxidation of **10** with PCC gave lactone **12**; however, it was very slow and inefficient. Alternatively, **12** was smoothly obtained in high yield in two steps via lactol **11**. With the dienophile **12** in hand, we attempted to react it with a few oxygenated butadienes reported in the literature.[4] Although some dienes afforded the corresponding aromatic compounds by the Diels–Alder reaction and subsequent hydrolytic workup, the resultant aromatic compounds needed to be transformed to **14** by additional steps. Thus, in order to synthesize **14** directly and efficiently from **12**, we prepared a novel diene **13**[5] from commercially available 4,4-dimethyl-1,3-cyclohexanedione in two steps. Fortunately, the Diels–Alder reaction of diene **13** with **12** proceeded successfully, accompanied by cycloreversion. The crude reaction mixture was exposed to the hydrolytic conditions to provide the desired phenolic compound **14**[6] in 81% yield as the sole regioisomer. Compound **14** is a key intermediate because it has all carbon atoms and functionalities requisite for the construction of the target compounds, and, besides, the protected secondary hydroxy group at the benzylic position is presumed to act as a stereodirecting group for the introduction of the other stereochemistries in the target molecules.

The next task was to construct the cyclohexane ring. The phenolic hydroxy group in **14** was protected with TIPS group to give **15**, which was subjected to the intramolecular Dieckmann condensation. A cyclized product was obtained, but, as it was not stable, it was directly converted to **16**. The stereochemistry at the ring junction of **16** was initially assigned on the basis of NOESY correlation, and subsequently confirmed by the *syn*-elimination of sulfoxide **18** affording olefin **19**. The reason for the introduction of a sulfenyl group was to create unsaturation for the subsequent epoxidation; however, direct conversion of **16** into olefin was presumed to be impossible because of the easy aromatization of the resultant olefin. Therefore, **16** was temporarily reduced with zinc borohydride[7] to give alcohol **17**,[6] whose configuration was assigned on the basis of NOESY correlation. Oxidation of **17** with *m*CPBA gave sulfoxides **18a** and **18b**, epimers at the sulfur atom, in 81 and 9% yield, respectively. Compounds **18a** and **18b** were refluxed separately in toluene to provide the desired olefin **19** in 89 and 76% yield, respectively.

The next phase of our syntheses was a stereoselective epoxidation of **19**. Since **19** was an α,β-unsaturated lactone, its epoxidation was first attempted by using alkaline hydrogen peroxide and *t*-butyl hydroperoxide. However, the aromatization by dehydration of **19** easily took place under these conditions; therefore, the desired epoxide was not obtained. Next we attempted the epoxidation with electrophilic epoxidizing agents (e.g. peroxyacids, dioxiranes); however, **19** utterly resisted epoxidation. The poor reactivity of **19** towards electrophilic epoxidizing agents was due to the carbonyl group which conjugated with the C–C double bond. Therefore, **19** was successively reduced with diisobutylaluminium hydride (DIBAL-H)[8] and $NaBH_4$ to give triol **20**, whose epoxidation with *m*CPBA in CH_2Cl_2 in the presence of the phosphate buffer (pH 7.9)[9] provided the epoxide **21**[6] as a single stereoisomer. The stereochemistry of the epoxy moiety in **21** was uncertain at this stage, although we expected that *m*CPBA would have reacted with **19** from the opposite side to the bulky TBDPS group.

We proceeded to the next task, reconstruction of the tetrahydrofuran ring. It was performed by the following steps: (i) selective mono-silylation of **21** with TBS group; (ii) protection of the other primary hydroxy group with TBDPS; (iii) selective removal of TIPS and TBS groups; (iv) oxidation of the hydroxy group at benzylic position with MnO_2; (v) tetra-*n*-propylammonium perruthenate (TPAP) oxidation[10] of the primary hydroxy group; (vi) removal of two TBDPS groups to give a yellowish compound. It exhibited identical properties with those reported for the natural product[1a] (^1H and ^{13}C NMR, and IR). Thus, the total synthesis of (±)-arthrinone (**1**) was achieved, and it revealed the stereochemistry of epoxide **21**.

The other target compounds, **2** and **3**, were synthesized from **22** as shown in Scheme 2. The primary hydroxy group of **22** was tosylated selectively by a conventional procedure to give **27** quantitatively. Direct conversion of **27** to **28** by selective removal of TIPS and TBS groups and subsequent cyclization was attempted using the same method as with **24** (Scheme 1). However, the yield of **28** was very low. This poor result seemed to be due to the long reaction time, which was required for complete removal of the TBS group of **27**. Therefore, we took an alternative two-step sequential method: tosylate **27** was treated with 5% ethanolic NaOH until **27** was not detected by TLC analysis to give the mono-desilylated compound, whose TBS group remained, along with **28**. A mixture of the crude products was heated in wet DMSO at 90°C[11] to afford **28** in moderate yield from **27**. Oxidation of **28** with MnO_2 afforded **29** quantitatively, which was then desilylated to provide (±)-dehydroxyarthrinone (**2**). On the other hand, treatment of **29** with sodium hydrogen telluride[12] was followed by desilylation to yield (±)-3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone (**3**). Synthetic **2** and **3** were identified by comparing their spectral data with those of the natural products[1b] (^1H and ^{13}C NMR, and MS).

Thus, we have accomplished the first total syntheses of (±)-arthrinone (**1**), (±)-1-dehydroxyarthrinone (**2**), and (±)-3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone (**3**) in a stereocontrolled manner. These syntheses unambiguously confirmed the relative stereochemistries of **2** and **3**. The asymmetric syntheses of **1**–**3** are now in progress.

References

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3. This reaction is helpful for our final goal, the asymmetric syntheses of **1**–**4**, because recently we found that the asymmetric oxyselenenylation of 2,3-dihydrofuran and subsequent oxidation afforded **6** in an enantioselective manner, which could give an optically active alcohol **7** by this rearrangement.
4. The dienes subjected to Diels–Alder reaction with **12** was as follows. (a) 1,1-Dimethoxy-3-trimethylsiloxy-1,3-butadiene: Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852–1856. (b) 1,3-Bis(trimethylsiloxy)-5,5-dimethylcyclohexa-1,3-diene: Ibuka, T.; Mori, Y.; Aoyama, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26*, 456–465. (c) 1,3-Dimethoxy-1-trimethylsiloxy-1,3-butadiene: Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455–3464. Only 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene did not react with **12**.
5. Diene **13** was prepared in the following way: 4,4-dimethyl-1,3-cyclohexanedione was treated with MeOH containing a catalytic amount of HCl to afford 6,6-dimethyl-3-methoxy-2-cyclohexenone in 65% yield. It was converted to **13** by treatment with LDA in THF at −78°C followed by quenching with TMSCl in 83% yield.
6. All new compounds gave satisfactory spectroscopic and analytical data. Representative data for selected compounds; **14**: IR ($CHCl_3$): 1770, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.04 (9H, s), 1.09 (3H, t, $J=7.2$ Hz), 2.15 (1H, dd, $J=9.0$, 17.6 Hz), 2.27 (1H, dd, $J=8.6$, 17.6 Hz), 2.83 (1H, m), 3.79 (3H, s), 4.06–4.24 (3H, m), 4.40 (1H, dd, $J=7.5$, 9.1 Hz), 5.81 (1H, d, $J=4.5$ Hz), 6.36 (1H, d, $J=2.7$ Hz), 6.89 (1H, d, $J=2.7$ Hz), 7.23–7.28 (2H, m), 7.34–7.47 (6H, m), 7.58–7.61 (2H, m), 11.62 (1H, s). Anal. calcd for $C_{31}H_{36}O_7Si$: C, 67.86; H, 6.61. Found: C, 67.59; H, 6.55. **17**: IR ($CHCl_3$): 3460, 1760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (9H, s), 1.07 (3H, s), 1.10 (9H, s), 1.12 (6H, s), 1.24–1.36 (3H, m), 3.11 (1H, ddd, $J=1.8$, 3.7, 9.6 Hz), 3.21 (1H, dd, $J=3.7$, 9.6 Hz), 3.58 (3H, s), 3.67 (1H, t, $J=9.6$ Hz), 4.38 (1H, d, $J=1.8$ Hz), 4.43 (1H, d, $J=12.4$ Hz), 5.30 (1H, d, $J=12.4$ Hz), 5.86 (1H, d, $J=2.3$ Hz), 6.35 (1H, d, $J=2.3$ Hz), 7.30–7.55 (11H, m), 7.70–7.73 (2H, m), 7.81–7.84 (2H, m). Anal. calcd for $C_{44}H_{56}O_6SSi_2$: C, 68.71; H, 7.34. Found: C, 68.49; H, 7.45. **21**: IR ($CHCl_3$): 3590, 3490 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 (9H, s), 1.14 (3H, s), 1.15 (3H, s), 1.16 (6H, s), 1.18 (6H, s), 1.29–1.41 (3H, m), 1.70 (1H, br-s), 2.75 (1H, br-s), 2.94 (1H, d, $J=10.9$ Hz), 3.44 (3H, s), 3.89 (1H, d, $J=12.8$ Hz), 4.15 (1H, br-d, $J=12.1$ Hz), 4.23 (1H, br-d, $J=12.1$ Hz), 4.25 (1H, br-d, $J=12.8$ Hz), 5.07 (1H, s), 5.58 (1H, d, $J=10.9$ Hz), 5.76 (1H, d, $J=2.3$ Hz), 6.37 (1H, d, $J=2.3$ Hz), 7.21–7.31 (4H, m), 7.35–7.41 (1H, m), 7.43–7.53 (3H, m), 7.75–7.78 (2H, m). Anal. calcd for $C_{38}H_{54}O_7Si_2$: C, 67.22; H, 8.02. Found: C, 66.85; H, 8.07.
7. Reduction of **16** with other reducing agents, such as $NaBH_4$, $Ca(BH_4)_2$, and n-Bu_4NBH_4, gave **17**; however, the desulfenylated by-product was also obtained. $Zn(BH_4)_2$ gave the best result.
8. The half-reduction of **19** with DIBAL-H afforded the corresponding lactol, but its epoxidation was fruitless.
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