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Base-catalyzed intramolecular condensation of tokinolide B☆

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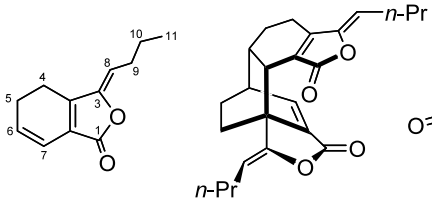
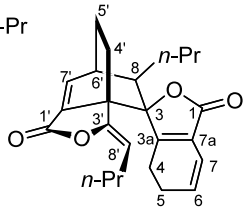
Abstract—The novel pentacyclic compound cyclotokinolide B was obtained from the natural phthalide tokinolide B under basic conditions, via the chemoselective γ-enol lactone opening followed by a Michael addition of the generated carbanion to the enone and subsequent equilibration. This result confirms that some dimeric phthalides undergo intramolecular cyclizations in basic media.

Several phthalides have been isolated from *Ligusticum porteri* (Apiaceae), an important medicinal herb widely used in northern Mexico and southwest USA for the treatment of various ailments.[1,2] The major chemical constituent of this species, *Z*-ligustilide (**1**) displays bioactivity in a broad number of screens, that include sedative evaluations, antispasmodic, antiasthmatic,[3] as well as antiviral and antimicrobial activities.[4] The chemical reactivity of phthalides have also been investigated,[4–6] and some years ago, a number of novel intramolecular carbon–carbon bond and oxygen–carbon bond forming reactions mediated by base were uncovered for the dimeric phthalide diligustilide (**2**).[7] In this context, we were interested in probing the intramolecular condensation towards other [π4*s*+π2*s*] dimeric phthalides with suitable fragments. Therefore, we attempted this transformation in tokinolide B (**3**),[8] a natural substance isolated from *L. porteri* and previously characterized from *Angelica acutiloba*[9] and *L. chuangxiong*,[10] and here we report the results.

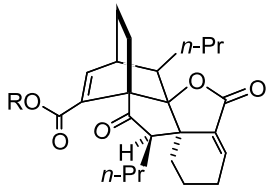


1 **2**



3

Treatment of tokinolide B (**3**) with NaOH in THF/MeOH[7] resulted in the product **4**,[11] named cyclotokinolide B, derived from intramolecular condensation according to the following spectroscopic evidence. The molecular formula of **4** ($C_{24}H_{30}O_5$, established by HRMS), indicated the addition of water with respect to the starting material (**3**, $C_{24}H_{28}O_4$), and the DEPT ^{13}C NMR data for **4** sorted the expected 24 signals into three carbonyls (a carboxylic acid, a lactone and a ketone), five quaternary carbons, five methines, nine methylenes and two methyl groups. The disappearance of the ^{13}C NMR signals assigned to the C(6)–C(7), C(3a)–C(7a) and C(3′)–C(8′) double bonds in the starting material (**3**) clearly indicated that these bonds were involved in the transformation. Treatment of **4** with ethereal diazomethane afforded the corresponding methyl ester **5**,[12] confirming the presence of the carboxylic acid. In addition, the signals for a ketone (IR: 1712 cm^{-1}; δ_C: 212.6) α- to a methine (δ_H 2.63, dd; δ_C 57.2) and for a γ-lactone (IR: 1755 cm^{-1}; δ_C: 168.8) conjugated with a trisubstituted olefin (δ_C: 132.1, 137.1; δ_H 6.91) suggested the formation of a cyclopentanone via C(8′)–C(3a) bond formation, to afford structure **4**. The *R*-relative configuration at C(8′) was determined by the observed crosspeak between H-8′ and *pro*-*R* H-4 in the NOESY spectrum of **4**, and the *R*-relative configuration at C(3a) was established by the diastereodifferentiated addition of the carbanion to C(3a). The structure and stereochemistry of this compound was confirmed by X-ray analysis.[13]



4 R = H

5 R = CH_3

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Figure 1 shows the 8*R*,8′*R* stereoisomer of compound **4**. Cyclotokinolide B is comprised of a pentacyclic skeleton with the five-membered rings adopting twisted conformations, while the conformation of the cyclohexene ring is intermediate between envelope and half-chair conformations. Both *n*-propyl chains are fully extended and point toward the same face of the molecule. That attached to the [2.2.2] bicyclic moiety displays an *exo*-orientation, while a bisectional orientation is observed for that attached to C8′. The carboxylic acid is essentially co-planar with the conjugated to the C7′–C7′A double bond (angle between planes: 2.8°) and has a close contact (O1′···C3′: 2.694(8) Å) with the carbonyl of the cyclopentanone.

A mechanistic rationale for the formation of **4** is presented in Scheme 1. The chemoselective nucleophilic attack of the hydroxide on the C(1) carbonyl affords the enolate (**A**). Although it is known that this nucleophilic entity **A**, can follow different pathways (*C*- and *O*- alkylation; or *C*- and *O*- acylation), in this case, Michael addition of the carbanion to the enone (a favored 5-*exo*-trigonal cyclization)[15] produces intermediate **B** and subsequent equilibration affords compound **4**.

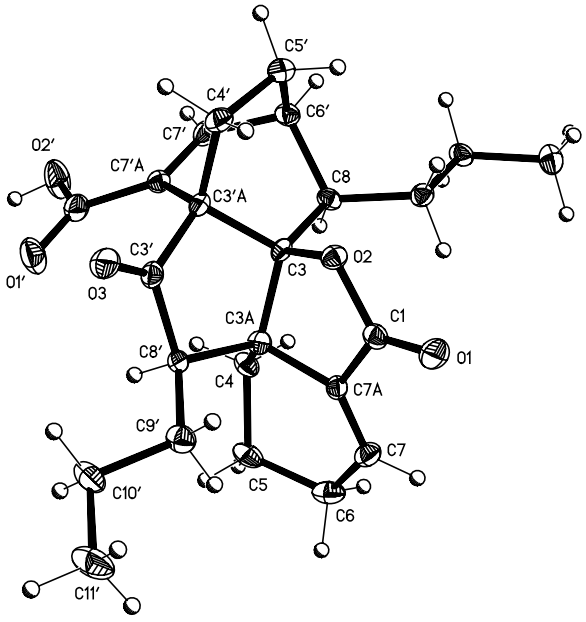
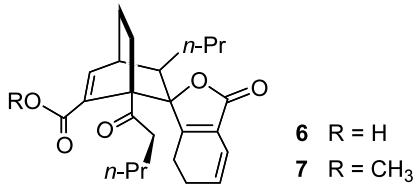


Figure 1. ORTEP-like view of cyclotokinolide B. Thermal ellipsoids at 20% probability level.

The hydrolysis of tokinolide B (Na_2CO_3, CH_3COCH_3/H_2O (1:1)) afforded the keto acid **6** (84%).[16] The γ-enol lactone of tokinolide B (**3**) is hydrolyzed easier in comparison with that of diligustilide (**2**), since under the same conditions, diligustilide affords lower yields of the corresponding keto acids.[5] It is interesting to note that the spiro-γ-lactone of **3** is unreactive under several hydrolytic conditions, due to the steric hindrance of both faces of the C(1) carbonyl group, exerted by the *n*-propyl at C(8) and the alkylidene substituent at C(3′). The same phenomenon is observed for angeolide, which is the C-8 epimer of **3**.[17] Treatment of tokinolide B (**3**) with sodium methoxide in MeOH afforded the corresponding keto ester (**7**)[18] at room temperature, which in turn did not afford the cyclization product. Refluxing this reaction mixture produced extensive decomposition. Therefore, the carboxylic acid at C(1′) is necessary for the cyclization reaction. A favorable complexation of the carboxylate and the enolate intermediate (**A**) with the cation (Na^+ or K^+) that favors the C(3a)–C(8′) σ-bond formation could explain this observation. Supporting this requirement, when the keto ester (**7**) is treated with the conditions used for the cyclization of tokinolide B (**3**), cyclotokinolide B (**4**) was obtained in similar yield, due to the initial hydrolysis of the methyl ester, followed by formation of the C(8′)–C(3a) bond. These results indicate that the intramolecular cyclizations of some dimeric phthalides may be considered a general feature for these substances.



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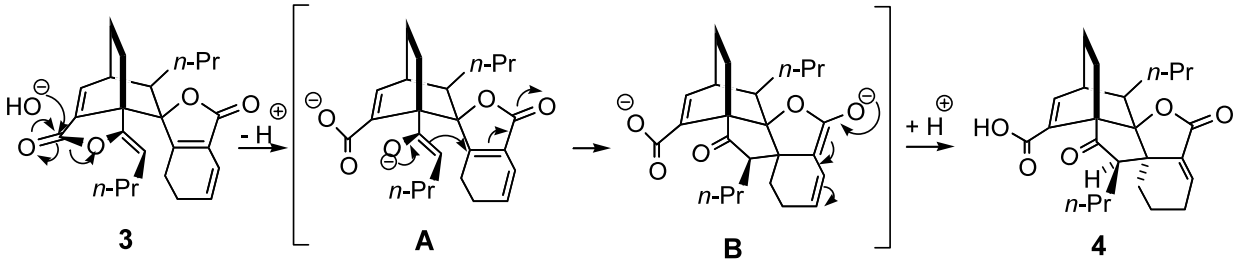

Scheme 1.

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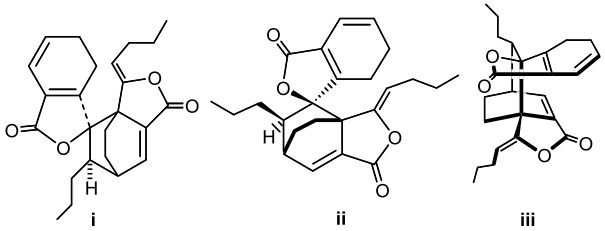
8. The structure of tokinolide has been published with different representations (i,[9] ii[10] and iii[6]), and we adopted here representation **3** to emphasize the feasibility of the formation of the new carbon–carbon σ bond.



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11. Preparation of cyclotokinolide B (**4**). Tokinolide B (**3**, 150.0 mg, 0.39 mmol) was treated with NaOH (205.7 mg, 5.14 mmol), in THF (10 mL) and MeOH (1 mL). After 2 h of refluxing under nitrogen, a more polar product was observed. The heterogeneous mixture was concentrated at reduced pressure. Methylene chloride was added and the organic phase was washed with diluted HCl (10%), with brine, dried with Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography eluted with *n*-hexane–EtOAc gradient and subsequent preparative TLC (*n*-hexane–EtOAc 1:1, twice) to afford cyclotokinolide B (**4**), as a white solid (90.0 mg, 57%). The same product was formed, although in lower yield (36%), by refluxing with KOH under the same conditions. **4**: mp: 172–173°C, R_f: 0.40 (CH_2Cl_2–MeOH, 95:5); UV (EtOH) λ_{max} nm (ε): 217 (18988). IR ($CHCl_3$) ν_{max} cm^{-1}: 2961, 2873, 1753, 1709, 1684, 1612, 1362, 1327, 1267, 943. ^1H NMR (500 MHz, $CDCl_3$; assignments by COSY and HETCOR) δ: 7.76 (1H, d, $J=7.0$ Hz, H-7′), 6.91 (1H, t, $J=3.8$, H-7), 2.92 (1H, m, H-6′), 2.63 (1H, dd, $J=9.0$ and 4.0 Hz, H-8′), 2.36 (1H, m, H-6*a*), 2.24 (1H, m, H-6*b*), 2.15 (1H, m, H-4′), 1.92 (2H, m, H-5, H-5′), 1.85 (1H, m, H-8), 1.72 (1H, m, H-10′), 1.59 (3H, m, H-4, H-5, H-9), 1.41 (5H, m, H-4, H-4′, H-9′, H-10, H-10′), 1.26 (1H, m, H-5′), 1.19 (1H, m, H-10), 0.99 (2H, m, H-9, H-9′), 0.88 (6H, 2t, $J=7.2$, H-11 and H-11′). ^{13}C NMR (125 MHz, $CDCl_3$, assignments by DEPT, HETCOR and FLOCK) δ: 212.6 (C-3′), 168.8 (C-1), 166.3 (C-1′), 154.3 (C-7′), 137.1 (C-7), 134.1 (C-7′a), 132.1 (C-7a), 93.9 (C-3), 57.2 (C-8′), 56.0 (C-3′a), 50.8 (C-3a), 42.0 (C-8), 35.7 (C-6′), 32.5 (C-4), 31.5 (C-9′), 28.8 (C-9), 24.7 (C-6), 23.9 (C-4′), 22.0 (C-10′), 20.7 (C-10), 17.7 (C-5), 16.1 (C-5′), 14.0 (C-11 and C-11′). EIMS *m*/*z* (rel. int.): 398 [M^+] (21), 380 (9), 356 (100), 338 (65), 309 (11), 296 (13), 271 (15), 253 (10), 207 (5), 190 (38), 189 (10), 149 (7), 91 (5), 79 (5). HRMS FAB$^+$ (PEG): Found 399.2193. Calcd for $C_{24}H_{30}O_5+H^+$ 399.2171 (MH^+).
12. Preparation of cyclotokinolide B methyl ester (**5**). To a warmed solution (55°C) of NaOH (1.25 g), H_2O (2 mL) and MeOH (6.5 mL), was added a solution of diazald (5.2 g) in ether (30 mL). The solution of diazomethane in ether (15 mL) was added (20 min) to a solution of **4** (20.0 mg, 0.05 mmol) in ether–MeOH (1:1, 5 mL). The reaction mixture was concentrated and the residue was purified by prep. TLC (*n*-hexane–EtOAc, 4:1) to give **5** (14 mg, 70%). Yellow oil, R_f: 0.40 (*n*-hexane–EtOAc 75:25). IR ($CHCl_3$) ν_{max} cm^{-1}: 2958, 2873, 1755, 1712, 1681, 1614, 1462, 1438, 1327, 1307, 1101, 1078, 974, 943. ^1H NMR (500 MHz, $CDCl_3$; assignments by COSY, HETCOR, HMBC, NOESY) δ: 7.59 (1H, d, $J=7.0$, H-7′), 6.90 (1H, t, $J=3.5$, H-7), 3.74 (3H, s, -OCH_3), 2.89 (1H, m, H-6′), 2.64 (1H, dd, $J=9.0$, 4.0, H-8′), 2.36 (1H, m, H-6), 1.73 (1H, m, H-6), 2.16 (1H, m, H-4′), 1.90 (2H, m, H-5, H-5′), 1.84 (2H, m, H-8, H-10′), 1.57 (3H, m, H-4, H-5, H-9), 1.42 (4H, m, H-4′, H-9′, H-10, H-10′), 1.25 (1H, m, H-5′), 1.19 (1H, m, H-10), 0.99 (2H, m, H-9, H-9′), 0.90 (3H, t, $J=7.0$, H-11′), 0.88 (3H, t, $J=7.0$, H-11). ^{13}C NMR (75 MHz, $CDCl_3$, assignments by DEPT, HETCOR, HMBC) δ: 212.9 (C-3′), 168.9 (C-1), 163.4 (C-1′), 151.2 (C-7′), 136.9 (C-7), 135.0 (C-7′a), 132.3 (C-7a), 94.2 (C-3), 57.3 (C-8′), 56.2 (C-3′a), 51.9 (CH_3OOC-), 50.8 (C-3a), 42.1 (C-8), 35.4 (C-6′), 32.4 (C-4), 31.6 (C-9′), 28.9 (C-9), 24.7 (C-6), 24.0 (C-4′), 22.1 (C-10′), 20.7 (C-10), 17.7 (C-5), 16.1 (C-5′), 14.2 (C-11′), 14.1 (C-11). EIMS *m*/*z* (rel. int.): 412 [M^+] (23), 280 (9), 370 (100), 352 (5), 338 (32), 309 (6), 296 (12), 285 (11), 254 (7), 221 (8), 190 (36), 189 (13), 149 (12), 105 (6), 91 (5), 77 (4), 55 (4).
13. X-Ray analysis data of compound **4**. All data were collected on a Siemens P4/PC diffractometer with graphite monochromated Mo Kα radiation ($\lambda=0.71073$ Å) using the θ–2θ scan technique at 293(2) K. The structure was solved and refined by using SHELXTL.[14] Compound **4** belongs to the monoclinic system, space group $P2_1/c$ with $a=15.755(2)$, $b=9.750(2)$, $c=16.983(2)$ Å and, $\beta=101.18(1)°$. The structure refines to $R=0.0766$ for reflections ($I>2\sigma$) and $R=0.1025$ for all data (3341) with a goodness-of-fit (GOF) of 1.028. Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 199813. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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16. Preparation of ketoacid **6**. To a solution of **3** (150 mg, 0.39 mmol) in acetone (15 mL) was added a solution of Na_2CO_3 in H_2O (10%, 15 mL, 14.15 mmol), and the mixture was stirred at reflux for 40 min. The reaction mixture was acidified with diluted HCl (10%, pH 4) and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuum. The resultant material was recrystallized (EtOAc–*n*-hexane) to afford **6** (132 mg, 84%) as a white solid (stored at 0–5°C and under nitrogen). Mp: 187–189°C, R_f: 0.30 (*n*-hexane–EtOAc, 3:2). IR ($CHCl_3$) ν_{max} cm^{-1}: 3514, 2960, 2875, 1747, 1706, 1689, 1651, 1612, 1435, 1276, 1072. ^1H NMR (200 MHz, $CDCl_3$; assignments by COSY, HETCOR) δ: 7.48 (1H, d, $J=7$, H-7′), 6.12 (1H, dt, $J=9.7$, 1.8, H-7), 5.86 (1H, dt, $J=9.7$, 3.9, H-6), 2.88 (1H, m, H-6′), 2.35 (2H, m, H-8′), 1.64 (1H, m, H-9′), 1.60 (1H, m, H-8), 1.42 (1H, m, H-9′), 1.25 (1H, m, H-10′), 1.08 (1H, m, H-10′), 0.86 (3H, t, $J=6.8$, H-11 or H-11′), 0.85 (3H, t, $J=6.8$, H-11 or H-11′). ^{13}C NMR (50 MHz, $CDCl_3$, assignments by DEPT and HETCOR) δ: 208.2 (C-3′), 170.7 (C-1), 169.8 (C-1′), 166.6 (C-3a), 149.5 (C-7′), 136.0 (C-7′a), 128.3 (C-6), 122.2 (C-7a), 116.4 (C-7), 90.2 (C-3), 58.5 (C-3′a), 42.6 (C-8), 40.9 (C-8′), 33.5 (C-6′), 27.5 (-CH_2-), 25.2 (2 -CH_2-), 22.6 (-CH_2-), 22.1 (-CH_2-), 21.9 (-CH_2-), 20.7 (-CH_2-), 18.2 (-CH_2-), 14.0 (C-11 or C-11′), 13.9 (C-11 or C-11′). EIMS *m*/*z* (rel. int.): 398 [M^+] (7), 191 (50), 190 (100), 148 (64), 120 (6), 105 (10), 77 (7), 55 (10).

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18. Preparation of the ketoester **7**. To a solution of **3** (76.5 mg, 0.2 mmol) in anh. MeOH (2 mL) was added a solution of sodium (50 mg) and MeOH (2.5 mL). After the mixture had been shaken for 1 h, a slightly less polar product than the starting material was formed. The reaction mixture was neutralized with diluted HCl (10%), the MeOH was evaporated at reduced pressure and the residue was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated in vacuum. The residue was purified by prep. TLC (*n*-hexane–EtOAc 85:15, twice) to afford **7** (42 mg, 51%) as a pale yellow oil (stored at 0–5°C and under nitrogen). R_f: 0.38 (*n*-hexane–EtOAc, 75:25). IR ($CHCl_3$) ν_{max} cm^{-1}: 2960, 2936, 2874, 1747, 1719, 1438, 1268, 1075. ^1H NMR (300 MHz, $CDCl_3$; assignments by COSY, HETCOR and FLOCK) δ: 7.26 (1H, d, $J=6.9$, H-7′), 6.10 (1H, dt, $J=9.6$, 1.8, H-7), 5.85 (1H, dt, $J=9.6$, 3.9, H-6), 3.69 (3H, s, CH_3O-), 2.83 (1H, m, H-6′), 2.51 (2H, m, H-8′), 1.65 (2H, m, H-8, H-9′), 1.42 (1H, m, H-9′), 1.25 (1H, m, H-10′), 1.06 (1H, m, H-10′), 0.86 (6H, 2t, $J=6.9$, H-11 or H-11′). ^{13}C NMR (75 MHz, $CDCl_3$, assignments by DEPT, HETCOR and FLOCK) δ: 208.5 (C-3′), 170.6 (C-1), 166.6 (C-3a), 165.7 (C-1′), 146.3 (C-7′), 136.9 (C-7′a), 128.4 (C-6), 122.3 (C-7a), 116.5 (C-7), 90.4 (C-3), 58.9 (C-3′a), 51.9 (CH_3O-), 42.7 (C-8), 40.9 (C-8′), 33.3 (C-6′), 27.7 (-CH_2-), 25.2 (2-CH_2-), 22.6 (-CH_2-), 22.0 (2 -CH_2-), 20.7 (-CH_2-), 18.3 (-CH_2-), 14.0 (C-11 or C-11′), 13.8 (C-11 or C-11′). EIMS *m*/*z* (rel. int.): 412 [M^+] (10), 222 (43), 190 (100), 189 (16), 165 (31), 148 (52).