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Synthetic studies toward the zoanthamine alkaloids: synthesis of the fully functionalized BC ring motif

Fatima Rivas, Subhash Ghosh and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0358, USA

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Abstract—A synthetic approach toward lactone **20**, representing the fully functionalized BC ring motif of the zoanthamine alkaloids, has been developed and is presented herein. The challenging C9 quaternary center of **20** was installed by a Wilkinson hydrogenation of enone **17** followed by construction of an α-bromo acetal and intramolecular cyclization exclusively from the α face of the BC ring system.
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Studies on the chemical constituents of marine zoanthids led to the identification of a new family of bioactive metabolites, collectively referred to as zoanthamine alkaloids.[1] These natural products are distinguished by a densely functionalized chemical motif, as exemplified by the structures of zoanthamine (**1**),[2] norzoanthamine (**2**),[3] and zoanthenol (**3**),[4] as well as by an impressive array of biological properties. For example, most family members were shown to inhibit thrombin-, collagen-, and arachidonic acid-induced inflammation of human platelets,[4] and exhibit a potent cytotoxicity against a variety of cancer cell lines.[5] In addition, zoanthamine **1** has been reported to inhibit phorbol myristate acetate-induced inflammation in mouse ear,[2] while norzoanthamine **2** was found to exhibit promising antiosteoporotic properties[6] (Fig. 1).

The combination of an unusual chemical structure and promising pharmacological potential has prompted the development of several synthetic routes toward the zoanthamine alkaloids[7,8] that have recently culminated in the first total synthesis of **2** by Miyashita et al.[9] One of the most challenging aspects of the zoanthamine structure is the C ring that features four contiguous stereocenters, three of which are quaternary. In continuation of our synthetic efforts,[10] we present here our studies toward the construction of a fully functionalized BC ring system of norzoanthamine.

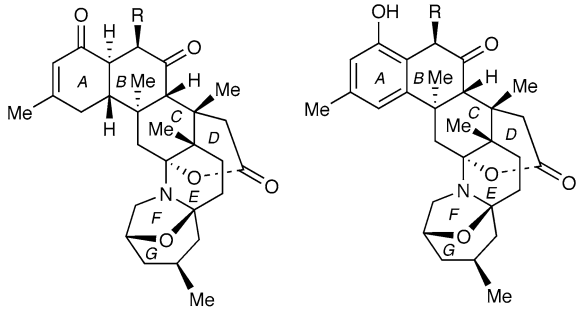

Figure 1. Selected structures of the zoanthamine alkaloids.

Compound **4**[10] (Scheme 1) was selected as the starting material of choice, since it is readily accessible and contains appropriate functionalities for conversion to the zoanthamine framework. At the onset of this study, we envisioned that conversion of **4** to a suitable β-keto lactone motif (such as **9**) would allow the construction of the C9 stereocenter with the desired configuration. To test this plan, compound **4** was transformed to ketone **5** via a three step sequence including acetonide deprotection, silylation of the primary hydroxyl group, and oxidation of the C9 alcohol (66% overall yield). Treatment of **5** with hydrazine produced the corresponding hydrazone that, upon reaction with I_2/Et_3N,[11] afforded vinyl iodide **6** (2 steps, 62% overall yield). A Pd(0)-catalyzed carbonylation[12] of **6**, followed by in situ deprotection of the primary silyl ether and lactonization, gave rise to tricycle **7** in 83% yield. Epoxidation

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* Corresponding author. Tel.: +1 (858) 822 0456; fax: +1 (858) 822 0386; e-mail: etheodor@ucsd.edu

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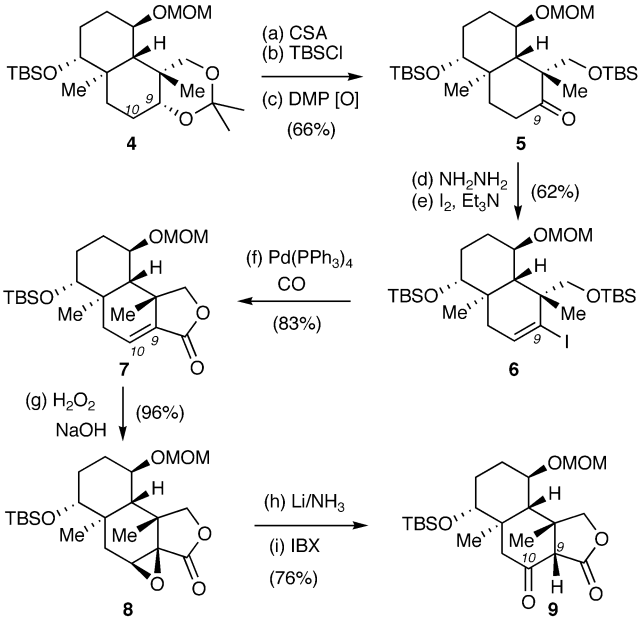
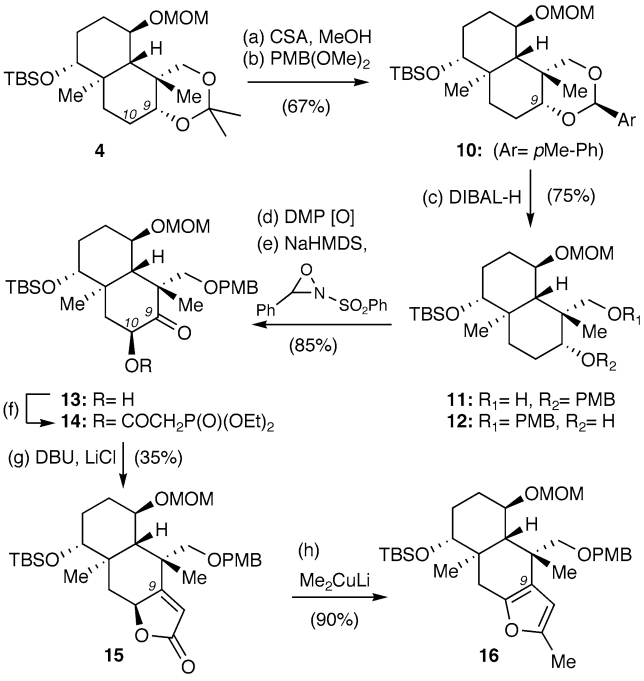


Scheme 1. Reagents and conditions: (a) 0.01 equiv of CSA, CH_2Cl_2–MeOH (10:1), 0 °C, 5 h, 70%; (b) 1.2 equiv of TBSCl, 2.5 equiv of imidazole, CH_2Cl_2, 0 to 25 °C, 12 h, 97%; (c) 1.3 equiv of Dess Martin periodinane, CH_2Cl_2, 0 to 25 °C, 5 h, 97%; (d) 10 equiv of NH_2NH_2, 15 equiv of Et_3N, Et_2O, 50 °C, 12 h; (e) 5 equiv of I_2, 10 equiv of Et_3N, Et_2O, 0 °C, 0.5 h, 62% yield (over two steps); (f) 0.01 equiv of $Pd(PPh)_4$, CO (1 atm), EtOH–THF (2:5), 1.0 equiv of Et_3N, 55 °C, 18 h, 83%; (g) 2.0 equiv of H_2O_2, 3 N NaOH, MeOH, 25 °C, 5 h, 96%; (h) 3.0 equiv of Li wire, liq. NH_3, THF–EtOH (10:1), −78 to 25 °C, 5 min, 83%; (i) 3.0 equiv of IBX, DMSO–CH_2Cl_2 (1:2), 50 °C, 18 h, 91%.



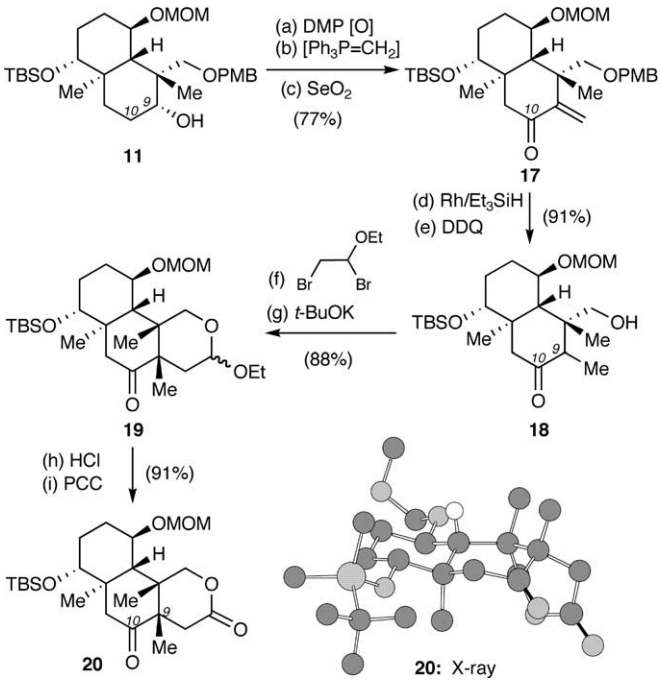
Scheme 2. Reagents and conditions: (a) 0.01 equiv of CSA, CH_2Cl_2–MeOH (10:1), 0 °C, 5 h, 70%; (b) 1.5 equiv of anisaldehyde dimethyl acetal, 0.01 equiv of CSA, CH_2Cl_2, 0 to 25 °C, 7 h, 96%; (c) 3.0 equiv of DIBAL-H, CH_2Cl_2, −78 to 25 °C, 2 h, 75%; (d) 1.3 equiv of Dess Martin periodinane, CH_2Cl_2, 0 to 25 °C, 97%; (e) 1.2 equiv of NaHMDS, 1.10 equiv of PhCH(O)NTs, THF, −78 °C, 1 h, 88%; (f) 1.2 equiv of $(EtO)_2P(O)CO_2H$, 2.0 equiv of DCC, THF, −78 to 25 °C, 6 h, 87%; (g) 2.0 equiv of LiCl, 2.0 equiv of DBU, THF, −78 to 25 °C, 4 h, 35%; (h) 2.0 equiv of CuI, 4.0 equiv of MeLi, −78 to 0 °C, THF, 1 h, 90%.

of the C9–C10 double bond proceeded exclusively from the β-face of the tricyclic motif and produced compound **8** in 96% yield. Reductive opening[13] of the epoxide functionality of **8** (Li/NH_3) and oxidation of the resulting alcohol formed β-keto lactone **9** in 76% yield.[14] Unfortunately, attempts to introduce the C9 methyl group during the reductive opening of epoxy lactone **8** were unsuccessful. Moreover, all efforts to methylate the C9 stereocenter of **9** met with failure. Screening of a large variety of bases (LDA, LiHMDS, KHMDS, *t*-BuOK, Cs_2CO_3, and K_2CO_3) with or without co-solvents (DMPU and HMPA) led to either O-methylation of the C10 carbonyl group or di-O-methylation.

The failure to methylate the C9 stereocenter of **9** under electrophilic alkylation conditions led us to explore nucleophilic alkylations, such as a conjugate addition in substrate **15** (Scheme 2). To evaluate this strategy, compound **4** was first converted to *p*-methoxy benzylidene acetal **10** (2 steps, 67% yield). Reductive cleavage of the acetal ring with DIBAL-H gave rise to PMB ethers **11** and **12** in a 6:1 ratio in favor of **11** and 75% combined yield. Oxidation of **11**, followed by α-hydroxylation (NaHMDS, Davis' oxaziridine),[15] proceeded exclusively from the β-face and produced α-hydroxyketone **13** in 85% combined yield. Esterification of **13** with $(EtO)_2P(O)CH_2CO_2H$ and DCC produced, after treatment with DBU and LiCl, the corresponding α,β-unsaturated lactone **15**.[14,16] Efforts to introduce the methyl group at the C9 position were unsuccessful, presumably due to the steric hindrance of the adjacent quaternary center. In fact, under forcing conditions, we observed formation of the methyl furan system **16**, that is proposed to arise via methylation at the carbonyl group of the lactone, followed by aromatization of the derived hemiketal.[17]

The above findings prompted us to explore the possibility of forming the C9 quaternary center via an intramolecular alkylation. To this end, alcohol **11** was converted to enone **17** via a three step sequence that included oxidation, Wittig olefination, and SeO_2-mediated allylic oxidation.[18] Wilkinson reduction of the exocyclic alkene,[19] followed by DDQ-mediated deprotection of the *p*-methoxybenzyl ether gave rise to ketone **18** in 91% combined yield. Alkylation of **18** with 1,2-dibromo-1-ethoxy-ethane produced the corresponding α-bromo acetal,[20] that upon exposure to *t*-BuOK[21] underwent intramolecular cyclization at the C9 position, affording tricycle **19** in 88% combined yield. To confirm the stereochemistry of the newly formed quaternary center, acetal **19** was subjected to acid catalyzed deprotection[22] and subsequent oxidation, producing lactone **20** in 91% yield.[14] A single crystal X-ray analysis of **20** established unambiguously the stereochemistry at the C9 center[23] (Scheme 3).

In conclusion, we describe a concise synthesis of the fully functionalized BC ring system of norzoanthamine



Scheme 3. Reagents and conditions: (a) 1.2 equiv of Dess Martin periodinane, CH_2Cl_2, 0 to 25 °C, 5 h, 98%; (b) 10.0 equiv of Ph_3PCH_3Br, 5.0 equiv of *t*-BuOK, THF, 18 h, 96%; (c) 6.2 equiv of SeO_2, 1,4-dioxane, 50 °C, 5 h, 81%; (d) 0.10 equiv of $(Ph_3P)_3RhCl$, 3.0 equiv of Et_3SiH, THF, 60 °C, 4 h; then 20.0 equiv of K_2CO_3, MeOH, 25 °C, 4 h, 100%; (e) 4.0 equiv of DDQ, CH_2Cl_2–H_2O (10:1), 0 to 25 °C, 3 h, 99%; (f) 40.0 equiv of *N*,*N*-dimethylaniline, 20 equiv of 1,2-dibromo-1-ethoxy-ethane, CH_2Cl_2, −78 to 25 °C, 12 h, 57%; (g) 2.0 equiv of *t*-BuOK, toluene, 65 °C, 12 h, 71%; (h) 0.1 M HCl, THF, 25 °C, 18 h, 77%; (i) 1.5 equiv of PCC, 4 Å MS, CH_2Cl_2, 0 to 25 °C, 18 h, 97%.

as well as our initial studies to install the C9 quaternary center. The successful approach rests upon an intramolecular cyclization of an α-bromo acetal on the C9 enolate center. Further elaboration of this motif to the synthesis of zoanthamine alkaloids is currently under investigation.

Acknowledgements

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14. All compounds gave satisfactory spectroscopic and analytical data. Selected data for compounds **9**, **15**, **16**, and **20** are included. Compound **9**: white solid; $R_f = 0.4$ (40%, EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, $J = 8.0$ Hz, 1H), 4.60 (d, $J = 7.2$ Hz, 1H), 4.49 (d, $J = 9.6$ Hz, 1H), 4.15 (d, $J = 9.6$ Hz, 1H), 3.71 (m, 2H), 3.38 (s, 3H), 2.60 (d, $J = 14.0$ Hz, 1H), 2.50 (d, $J = 13.2$ Hz, 1H), 2.17 (m, 1H), 1.78 (d, $J = 10.8$ Hz, 1H), 1.70 (m, 1H), 1.30–1.65 (m, 5H), 0.98 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 174.0, 95.8, 81.9, 78.8, 75.2, 73.6, 56.6, 51.7, 49.4, 47.8, 44.8, 31.4, 29.4, 26.2, 24.3, 18.4, 14.6, −3.6, −4.3; HRMS calcd for $C_{22}H_{39}O_6Si$ (M+H$^+$) 427.2516. Found: 427.2519. Compound **15**: colorless oil; $R_f = 0.35$ (20%, EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.0$ Hz, 2H), 5.79 (s, 1H), 4.78 (dd, $J = 6.0$, 12.4 Hz, 1H), 4.62 (d, $J = 6.8$ Hz, 1H), 4.51 (d, $J = 6.8$ Hz, 2H), 4.43 (d, $J = 12.0$ Hz, 1H), 4.31 (d, $J = 12.0$ Hz, 1H), 3.80 (s, 3H), 3.71 (m, 1H), 3.61 (d, $J = 8.8$ Hz, 1H), 3.47 (d, $J = 9.2$ Hz, 1H), 3.32 (s, 3H), 3.12 (dd, $J = 4.8$, 10.8 Hz, 1H), 2.55 (d, $J = 5.6$, 12 Hz, 1H), 2.16 (br d, $J = 11.6$ Hz, 1H), 1.05–1.80 (m, 8H), 0.60–1.05 (m, 12H), 0.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 173.6, 159.6, 129.9, 129.6, 114.9, 114.1, 96.3, 79.2, 78.7, 76.3, 73.1, 71.9, 56.5, 56.4, 55.6, 45.1, 44.6, 41.9, 32.1, 29.1, 26.1, 26.0, 18.2, 14.9, −3.8, −4.6; HRMS calcd for $C_{31}H_{48}NaO_7Si$ (M+Na$^+$) 583.3067. Found: 583.3065. Compound **16**: colorless oil; $R_f = 0.6$ (20%, EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.02 (s, 1H), 4.59 (d, $J = 7.2$ Hz, 1H), 4.52 (d, $J = 6.8$ Hz, 1H), 4.47 (d, $J = 12.4$ Hz, 2H), 4.37 (d, $J = 12.4$ Hz, 1H), 3.81 (s, 3H), 3.60 (m, 3H), 3.33 (s, 3H), 2.61 (d, $J = 16.4$ Hz, 1H), 2.10–2.35 (m, 4H), 1.20–1.65 (m, 9H), 0.89 (m, 12H), 0.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 149.3, 146.4, 131.4, 129.2, 123.9, 113.8, 106.9, 96.5, 79.5, 74.2, 73.3, 56.3, 55.5, 54.7, 42.7, 39.4, 37.1, 31.8, 30.1, 29.9, 29.1, 26.1, 18.3, 14.8, 13.9, −3.7, −4.6; HRMS calcd for $C_{32}H_{51}O_6Si$ (M+H$^+$) 559.3455,. Found: 559.3457. Compound **20**: white crystals; $R_f = 0.3$ (65%, Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, 7.2 Hz, 1H), 4.57 (d, $J = 7.2$ Hz, 1H), 4.23 (d, $J = 11.6$ Hz, 1H), 4.05 (d, $J = 11.6$ Hz, 1H), 3.75 (m, 1H), 3.47 (d, $J = 17.6$ Hz, 1H), 3.39 (s, 3H), 3.36 (m, 1H), 2.41 (s, 2H), 2.22 (m, 1H), 2.18 (s, 2H), 2.0 (d, $J = 10.8$ Hz, 1H), 1.70 (m, 1H), 1.56 (s, 3H), 1.50 (m, 1H), 1.43 (s, 3H), 1.25 (s, 3H), 0.87 (s, 9H), 0.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 172.6, 95.6, 78.9, 74.6, 71.4, 56.9, 52.8, 52.4, 48.1, 45.0, 44.9, 35.6, 31.2, 31.1, 29.1, 26.0, 25.0, 23.9, 18.3, 14.5, −3.8, −4.5; HRMS calcd for $C_{24}H_{43}O_6Si$ (M+H$^+$), 455.2829. Found: 455.2828.
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23. CCDC-269731 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).