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Convergent synthesis of the ABC-ring moiety of zoanthenol: intramolecular Mizoroki–Heck reaction

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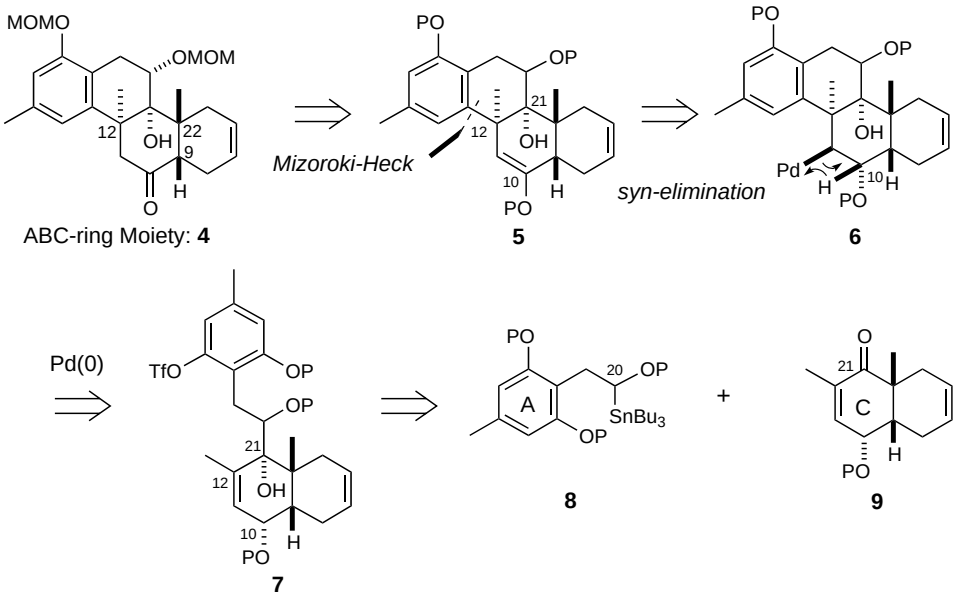
Abstract—The highly congested ABC-ring moiety of zoanthenol was stereoselectively synthesized via an alkoxylithium-mediated coupling between the A-ring and C-ring moieties followed by a Mizoroki–Heck-type ring closure.

Zoanthamine alkaloids, which are isolated from the marine zoanthid *Zoanthus sp*., have densely functionalized heptacyclic structures and interesting biological activities. Zoanthamine (**1**) exhibits inhibitory activity towards phorbol myristate-induced inflammation,[1] while norzoanthamine (**2**) suppresses the decrease in bone weight and strength in overiectomized mice without serious side effects.[2] Norte and co-workers recently reported zoanthenol (**3**), which possesses an aromatized A-ring, as a new member of this family.[3] The unique structural topologies and biological activities of these alkaloids have attracted increasing attention among synthetic chemists.[4,5] Notably, the groups of Tanner[5a] and Williams[5d] have reported synthetic approaches to the AB(C)-ring skeleton of zoanthamines via intramolecular Diels–Alder reactions.

A critical problem in the total synthesis of the zoanthamines is the stereo-controlled construction of the three consecutive quaternary carbon centers (C9, C12 and C22) in the C-ring. A strategy to incorporate the angular methyl groups at C9 and C22 has been developed.[4a] However, the quaternary ring junction at C12 remained to be constructed; our retrosynthetic analysis is outlined in Scheme 1.[6] We envisioned that an intramolecular Mizoroki–Heck cyclization[7] of **7** in a



Scheme 1.

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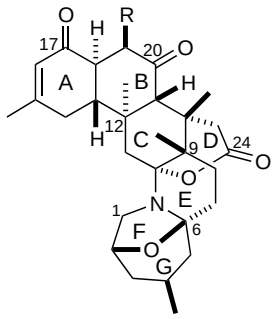
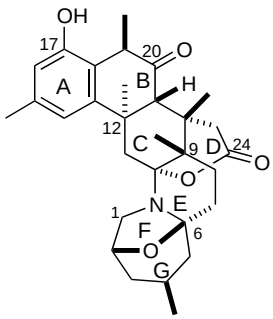


Zoanthamine: **1** (R = Me)
Norzoanthamine: **2** (R = H)

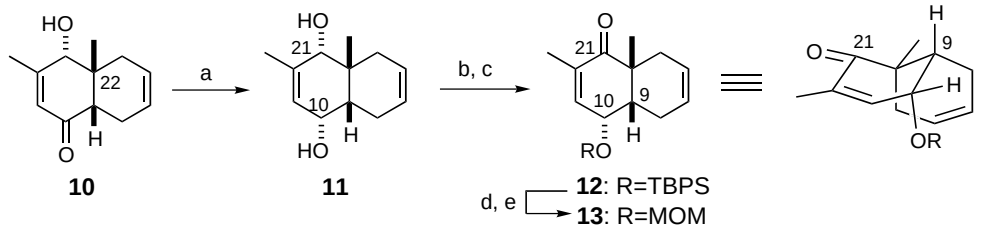


Zoanthenol: **3**

6-exo manner could afford the enol ether (**5**), which would be transformed into the ABC-ring moiety (**4**). To conduct this ring closure from the β-face of the tri-substituted olefin with *syn* palladium hydride elimination from **6**, the stereogenic centers at C21 and C10 of **7** must be controlled. The key precursor (**7**) would be synthesized by combining the A-ring (**8**) and C-ring moieties (**9**). In this paper, we describe a convergent and stereoselective synthesis of the ABC-ring moiety (**4**) of **3** based on a Mizoroki–Heck type ring closure.

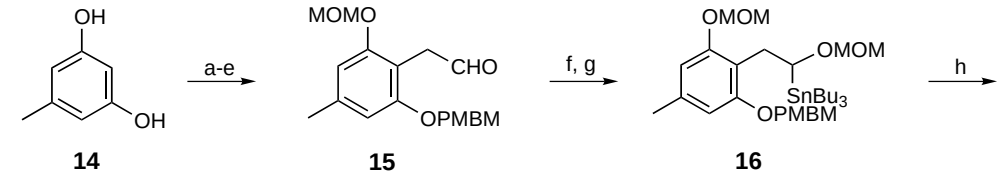
The synthesis of the C-ring began with **10** which possesses the C22 angular methyl group, and which was readily available from 2,6-dimethylphenol as reported earlier (Scheme 2).[4a] The enone (**10**) was reduced with DIBAL-H diastereoselectively to give diol (**11**). Selective protection of the C10 alcohol as its *t*-butyldiphenylsilyl (TBPS) ether and subsequent oxidation of the C21 alcohol yielded enone (**12**).

We then synthesized the A-ring moiety as shown in Scheme 3. Commercially available orcinol (**14**) was converted to aldehyde (**15**) via protection, allylation[8] and oxidation. Addition of tributylstannyllithium to **15** followed by protection gave α-alkoxystannane[9] (**16**) in good yield. The α-alkoxylithium species generated from **16** reacted with **12** from the β-face[10,11] in a highly stereo-controlled manner to give the adduct (**17**) as an inseparable C20 diastereomeric mixture (2:1).[12] How-



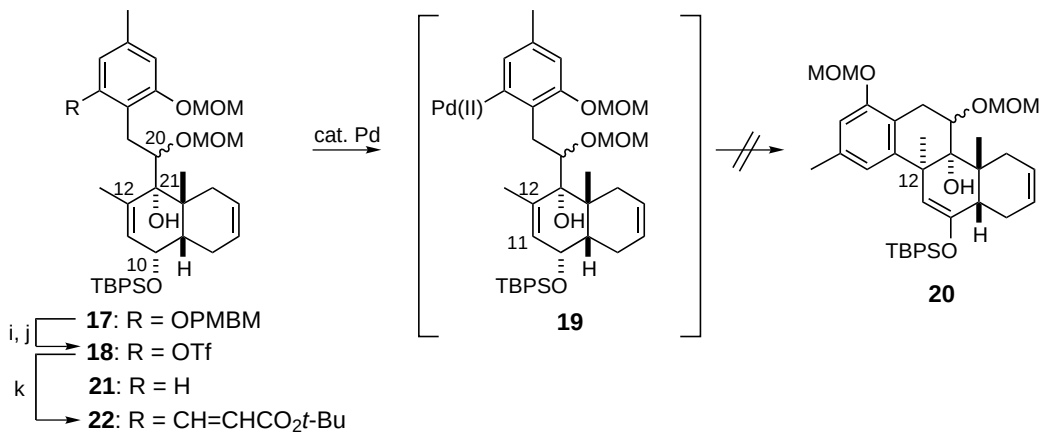
10 **11**

Scheme 2. *Reagents and conditions:* (a) DIBAL-H, THF, −78°C, 84% (6:1); (b) TBPSCI, imidazole, DMF, rt; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 99% (2 steps); (d) TBAF, THF, reflux, 98%; (e) MOMCl, *i*-Pr_2NEt, $(CH_2Cl)_2$, 50°C, 87%.



14 **15** **16**

PMBM = $CH_2OCH_2C_6H_4p$-OMe



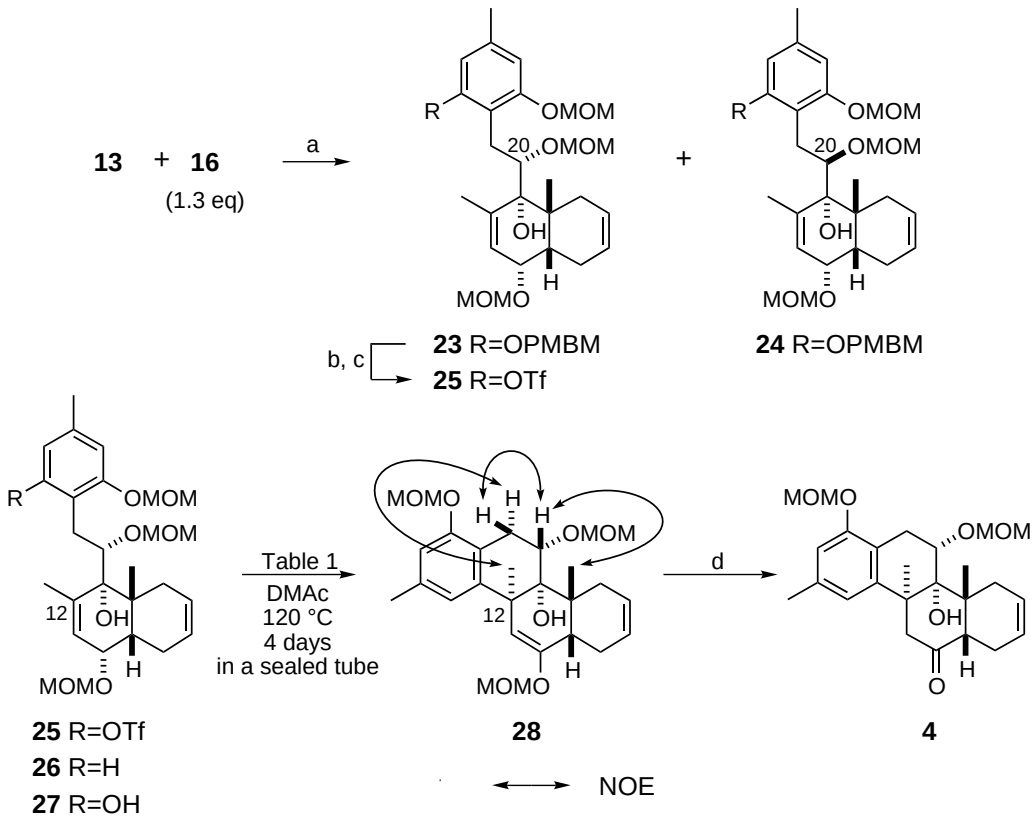
19 **20**

Scheme 3. *Reagents and conditions:* (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 61%; (b) PMBMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 79%; (c) *n*-BuLi, hexane, 0°C then allyl bromide, rt, 62%; (d) OsO_4, NMO, *t*-BuOH–H_2O (1:1), 89%; (e) $NaIO_4$, THF–H_2O (1:1), 80%; (f) Bu_3SnLi, THF, −78°C; (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 84% (2 steps); (h) *n*-BuLi, **12** (13 equiv.), THF, −78°C, 82% (2:1); (i) DDQ, CH_2Cl_2–H_2O (10:1), 62%; (j) Tf_2O, Et_3N, CH_2Cl_2, −78°C, 85%; (k) CH_2=$CHCO_2t$-Bu, $Pd_2(dba)_3$ (10 mol%), dppb (40 mol%), KOAc, DMAc, 100°C, 56%.

ever, Mizoroki–Heck reaction of triflate (**18**) did not proceed and the major product was the reduced product (**21**) under various internal cyclization conditions. We reasoned that the cyclization of its Pd(II) intermediate (**19**) was prevented sterically by the neighboring TBPS ether group,[13] as substantiated by the formation of an intermolecular adduct (**22**) when the reaction was conducted in the presence of *t*-butyl acrylate.

Thus, the C10 alcohol was protected by the less-demanding MOM group (**13**) (Scheme 2). The ketone (**13**) was coupled with **16** to afford a separable 2:1 mixture of **23** and **24** (Scheme 4). The major diastereomer (**23**) was subsequently converted into triflate (**25**). An intramolecular Mizoroki–Heck reaction of **25** proceeded using $Pd_2(dba)_3$–dppb as the catalyst system.[14,15] Optimized conditions are listed in Table 1. More than 20 mol% of $Pd_2(dba)_3$–dppb appeared necessary to realize this reaction in an appreciable yield, because a hydrolyzed product (**27**) was otherwise produced (Entry 3). An optimal yield of **28** (43%) was attained in the presence of 1,2,2,6,6-pentamethyl piperidine (PMP),[16] instead of KOAc, which suppressed the formation of the reduction product (**26**) (Entry 4).[17,18] The stereochemistry of **28** was unambiguously determined by NOE experiments. Finally, the enol ether (**28**)[19] was hydrolyzed to afford the targeted ABC-ring moiety (**4**).

In conclusion, the key intermediate (**25**) was synthesized via a stereo-controlled coupling reaction between the A-ring (**16**) and C-ring (**13**) segments. The subsequent intramolecular Mizoroki–Heck reaction of **25** constructed the B-ring and simultaneously introduced the C12 quaternary center of **28**. The convergent synthetic route presented herein offers an efficient strategy for the total synthesis of **3** and further synthetic efforts in this direction will be reported in due course.

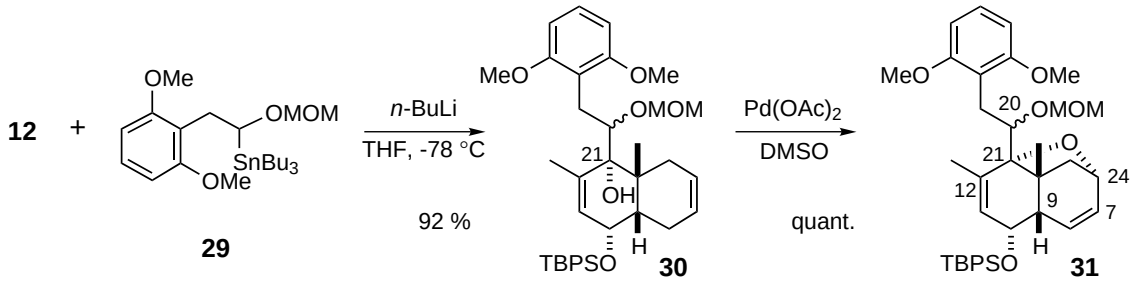


Scheme 4. *Reagents and conditions:* (a) *n*-BuLi, THF, −78°C, **23** (58%), **24** (32%); (b) lithium(di-*t*-butylbiphenyl), THF, −78°C, 90%; (c) Tf_2O, Et_3N, CH_2Cl_2, −78°C, 85%; (d) 1 N HCl aq., THF, rt, 89%.

Table 1. Intramolecular Mizoroki–Heck reaction of **25**[a]

Entry	Pd complex (equiv.)	Base (equiv.)	Yield of **28** (%)	Yields of products (%)
1	$Pd(OAc)_2$ (0.5)–PPh_3 (2)	KOAc (10)	20	**26** (7)
2	$Pd_2(dba)_3$ (0.25)–dppb (1)	KOAc (10)	33	**26** (33)
3	Pd_2 $(dba)_3$ (0.1)–dppb (0.4)	KOAc (10)	15	**26** (15), **27** (30)
4	$Pd_2(dba)_3$ (0.25)–dppb (1)	PMP (5)	43	**26** (trace)

[a] Carried out in *N*,*N*-dimethylacetamide (DMAc) at 120°C for 2 days in a sealed tube.



Scheme 5. Selected data for **31** (major diastereomer at C20): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.71 (4H, m, TBPS), 7.42 (6H, m, TBPS), 7.09 (1H, t, $J=8.5$ Hz, Ar), 6.48 (2H, d, $J=8.5$ Hz, Ar), 6.08 (1H, br, 7-H), 5.93 (1H, dd, $J=9.5$, 1.5 Hz, 8-H), 5.39 (1H, d, $J=1.5$ Hz, 11-H), 4.72 (1H, br, 10-H), 4.37 (1H, d, $J=6.5$ Hz, MOM), 4.25 (1H, d, $J=6.5$ Hz, MOM), 4.19–4.14 (2H, m, 20-H, 24-H), 3.75 (6H, s, OMe), 3.06 (1H, dd, $J=14$, 12 Hz, 19-H), 2.70 (3H, s, MOM), 2.36–2.28 (3H, m, 9-H, 19-H, 23-H), 1.96 (3H, s, 12-CH_3), 1.52 (1H, d, $J=10$ Hz, 23-H), 1.33 (3H, s, 22-CH_3), 1.12 (9H, s, TBPS).; MALDI-TOF MS Calcd for $C_{40}H_{50}NaO_6Si$ (M+Na) 677.3275, Found 677.3496.

Acknowledgements

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10. Attack of alkoxylithium species from the β-face was supported by a model reaction as shown in Scheme 5. The ketone (**12**) was reacted with **29**, and the alcohol so formed cyclized quantitatively to form the ether (**31**) when treated with $Pd(OAc)_2$. For a similar cyclization of *cis*-decalin derivatives, see: Pratt, D. V.; Hopkins, P. B. *J. Org. Chem.* **1988**, *53*, 5885.
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14. Reactions using other ligands [including PPh_3, 1,3-bis-(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)ethane (dppe), 1,5-bis(diphenyphosphino)-pentane, 1,1′-bis(diphenylphosphino)ferrocene (dppf)] provided only small amounts of product (**28**) and larger amounts of the reduced product (**26**).
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18. Addition of LiCl[16] did not suppress the formation of **27**.
19. Data for **28**: ^{1}H-NMR (500MHz, $CDCl_3$) δ 6.89 (1H, s, 14-H), 6.73 (1H, s, 16-H), 5.81 (1H, m, 7-H), 5.66 (1H, m, 24-H), 5.16 (2H, s, MOM), 5.10 (1H, d, $J=6.5$ Hz, MOM), 5.05 (1H, d, $J=6.5$ Hz, MOM), 5.03 (1H, s, 11-H), 4.94 (1H, d, $J=7$ Hz, MOM), 4.81 (1H, d, $J=7$ Hz, MOM), 3.94 (1H, dd, $J=8$, 6 Hz, 20-H), 3.62 (1H, s, OH), 3.49 (3H, s, MOM), 3.47 (1H, dd, $J=16$, 6 Hz, 19-Hβ), 3.47 (3H, s, MOM), 3.47 (3H, s, MOM), 2.76 (1H, dd, $J=16$, 8 Hz, 19-Hα), 2.65 (1H, m, 23-H), 2.50 (1H, m, 8-H), 2.39 (1H, m, 8-H), 2.29 (3H, s, 15-CH_3), 2.04 (1H, dd, $J=9.5$, 6 Hz, 9-H), 1.77 (1H, m, 23-H), 1.37 (3H, s, 12-CH_3), 0.60 (3H, s, 22-CH_3); ^{13}C-NMR (125MHz, $CDCl_3$) δ 153.9 (C17), 152.3 (C10), 147.7 (C13), 136.9 (C15), 127.5 (C24), 125.5 (C7), 119.4 (C18), 118.9 (C16), 112.5 (C14), 104.9 (C11), 95.7 (MOM), 94.9 (MOM), 93.4 (MOM), 77.7 (C21), 74.9 (C20), 56.4 (MOM), 56.1 (MOM), 55.7 (MOM), 45.4 (C12), 43.7 (C9), 41.2 (C22), 33.5 (C23), 29.5 (C8), 27.9 (C22-CH_3), 27.4 (C12-CH_3), 26.5 (C19), 21.9 (C15-CH_3); FT-IR (film) ν 3529, 2927, 1686, 1610, 1584, 1465, 1377, 1286, 1217, 1151, 1027, 922, 846, 772 cm^{-1}; MALDI-TOF-MS Calcd for $C_{27}H_{38}NaO_7$ (M+Na) 497.252, Found 497.253.