Synthetic Study of Zoanthamine Alkaloids: The C-ring Model Possessing Three Consecutive Quaternary Carbons

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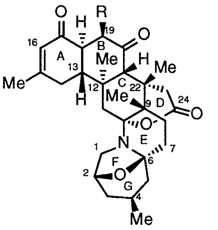
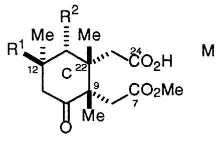
Stereo-controlled construction of the C-ring model (**4**) of zoanthamine alkaloids was achieved via a SmI$_2$-mediated Simmons-Smith reaction.

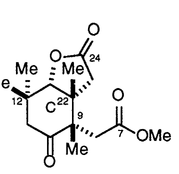
Zoanthamine alkaloids, a family of marine metabolites, can be isolated from the zoanthid *Zoanthus* sp.[1] Zoanthamine (**1**) exhibited inhibitory activity toward phorbol myristate-induced inflammation.[1b] Recently, norzoanthamine (**2**) has been shown to suppress IL-6 production and decrease bone weight and strength in overiectomized mice without serious side effects.[2] These zoanthamine alkaloids have a unique skeleton that consists of a complex amino acetal and δ-lactone in the D-G ring and three consecutive quaternary carbon centers in the C ring (C9, C12 and C22).[3] Because of the unique structural topology and biological activities, these compounds have attracted increasing attention among synthetic chemists.[4] We report herein the stereoselective construction of a model compound (**4**) for the C-ring segment (**3**), which should provide an efficient strategy for the total synthesis of the zoanthamine alkaloids.



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



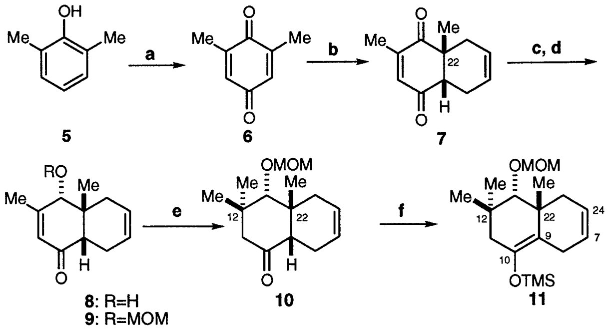
C-Ring Segment (**3**)



C-Ring Moiety (**4**)

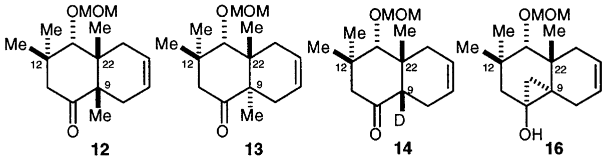
A commercially available 2,6-dimethylphenol (**5**) was oxidized to 2,6-dimethylbenzoquinone (**6**) with molecular oxygen in the presence of catalytic amounts of CuCl$_2$ (5 mol%) and (NH$_2$OH)$_2$·H$_2$SO$_4$ (10 mol%) in *t*-BuOH (Scheme 1).[5] Diels-Alder reaction of **6** with 1,3-butadiene was promoted by BF$_3$·Et$_2$O to give enedione (**7**) possessing the C22 angular methyl group in 85% yield from **5**.[6] Regio- and stereo-selective reduction of **7** gave an allylic alcohol (**8**) as a single product,[7] which was then protected as a methoxymethyl ether (**9**) Conjugate addition of lithium dimethylcupurate to **9** took place smoothly in the presence of TMSCl[8] to afford **10** in 75% yield after hydrolysis of resulting enol silyl ether. Thus, the angular methyl group at C12 was easily constructed by utillizing organocuprate. Thermodynamically controlled enolization proceeded in good yield upon treatment of **10** with TMSI and HN(TMS)$_2$[9] to give enol silyl ether (**11**).

Scheme 1.

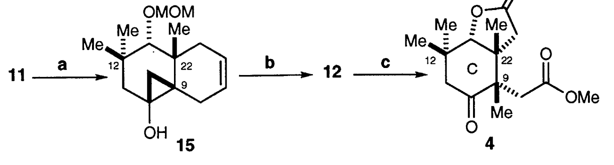


(a) CuCl$_2$ (5 mol%), (NH$_2$OH)$_2$·H$_2$SO$_4$ (10 mol%), O$_2$ (5 atm), *t*-BuOH, 40 °C. (b) 1,3-butadiene, BF$_3$·Et$_2$O, Et$_2$O, 0 °C, 85% (2 steps). (c) NaBH$_4$, MeOH, 0 °C, 95%. (d) MOMCl, (*i*-Pr)$_2$NEt, (CH$_2$Cl)$_2$, 50 °C, 91%. (e) Me$_2$CuLi, TMSCl, Et$_2$O, then TBAF, THF, 0 °C, 75%. (f) TMSI, HN(TMS)$_2$, 92%.

We then attempted angular methylation of **11** to construct the C9 quaternary carbon. The enol silyl ether (**11**) was treated with MeLi in ether in the presence of HMPA at 0 °C and then with excess methyl iodide at the same temperature for 12 h to give an unfavorable mixture of *cis*-dimethyl decalone (**12**) and *trans*-dimethyl decalone (**13**) in 8% and 25% yield, respectively. This stereoselectivity is intriguing, because *cis*-decalone (**14**) was obtained exclusively when the enolate intermediate was quenched with D$_2$O. The problem was solved by applying the Simmons-Smith reaction (Scheme 2). The reaction of the lithium enolate of **11** with SmI$_2$/ClCH$_2$I[10] at -78 °C gave successfully a 3:1 mixture of cyclopropanol (**15**) and (**16**).[11] When ZnEt$_2$/CH$_2$I$_2$[12] was used, the cyclopropanation did not proceed regioselectively at the C9-C10 double bond. The C7-C24 double bond also reacted competitively. Acid hydrolysis of the 3:1 mixture of **15** and **16** yielded the *cis*-dimethyldecalone (**12**) in 61% yield. After the *trans*-isomer (**13**) was removed, the double bond of **12** was oxidatively cleaved. The resulting dicarboxylic acid was heated with *p*-TsOH in toluene followed by treatment with diazomethane to give the lactonic ester (**4**).[13] Thus, the two carboxyl groups can be effectively differentiated for further manipulation. The stereochemistry of **4** was confirmed by N.O.E. experiments.



Scheme 2.



(a) MeLi, DME-HMPA (3:1), then SmI$_2$, ClCH$_2$I, -78 °C to -20 °C. (b) cat. *p*-TsOH, CH$_2$Cl$_2$, rt, 61% (2 steps). (c) 1) RuCl$_3$·nH$_2$O, NaClO$_4$, CCl$_4$-CH$_3$CN-pH7 phosphate buffer (1:1:1), rt; 2) *p*-TsOH, toluene, 80 °C; 3) CH$_2$N$_2$, Et$_2$O, 57% (3 steps).

In conclusion, the consecutive quaternary centers of the C-ring model (**4**) has been successfully constructed utilizing TMSCl-assisted cuprate addition and $SmI_2/ClCH_2I$-mediated Simmons-Smith reaction. The present synthesis should provide a useful strategy for synthesizing the critical C-ring moiety (**3**) of zoanthamines.

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References and Notes

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11 Although the stereoselectivity was improved to 4.3:1 when CH_2I_2 was used in place of $ClCH_2I$, the reaction was incomplete and resulted in the lower yield of **12**, as reported by Molander and co-workers: see ref 10b.

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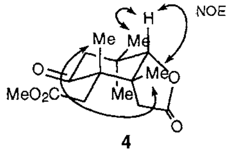
13 Data for **4** : IR (neat) ν 1785, 1738, 1717 cm^{-1}; ^1H-NMR (500MHz,$CDCl_3$) δ 4.09 (s, 1H), 3.65 (s, 3H), 2.98 (d, J = 15.0 Hz, 1H), 2.64 (d, J = 13.0 Hz, 1H), 2.60 (d, J = 17.5 Hz, 1H), 2.45 (d, J = 13.0 Hz, 1H), 2.39 (d, J = 15.0 Hz, 1H), 2.27 (d, J = 17.5 Hz, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H); HRMS: Calcd for $C_{15}H_{22}O_5$ 282.1467. Found 282.1463.



4