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A Pauson–Khand and Ring-Expansion Approach to the Aquariane Ring System

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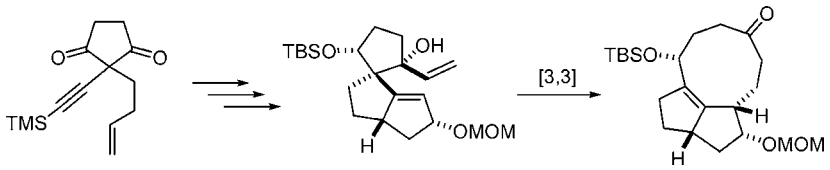
ABSTRACT



The carbocyclic ring system of the aquariolide diterpenes has been synthesized by two routes involving a diastereoselective Pauson–Khand reaction and subsequent ring expansion. In one route, a tetracyclic enone was elaborated to generate the nine-membered ring by Grob fragmentation. In the second approach, a spirocyclic tricycle underwent a facile anionic oxy-Cope rearrangement to complete the synthesis of the desired ring system.

The aquariolides (Figure 1) are cyclic diterpenes that were isolated from *Erythropodium caribaeorum.* Andersen and co-workers first identified aquariolide A (**1**) from cultured specimens of this gorgonian in 2002.[1] Aquariolides A, B (**2**), and C (**3**) were later isolated from animals growing in the wild.[2] The distinguishing feature of these natural products is the "aquariane" skeleton (**4**), which includes a nine-membered ring fused to two five-membered rings. *E. caribaeorum* has been a rich source of briarane ditepenes,[3] and the aquariolides are believed to arise biosynthetically from a briarane precursor by a di-π-methane rearrangement and subsequent vinyl−cyclopropane rearrangement.[2] In a very limited biological assay, aquariolides B and C exhibited moderate in vitro cytotoxicity toward human breast cancer MCF-7 cells.[2] As a prelude to a synthesis of **1**, the novel ring system has been prepared, and the salient results of this endeavor are communicated here.

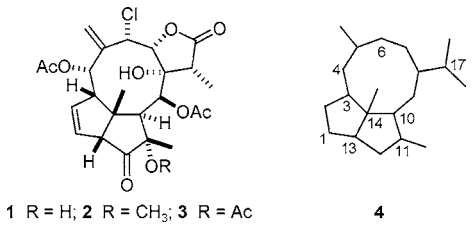


Figure 1. The aquariolides and the aquariane skeleton.

The enone moiety of the target compound **5** would provide the opportunity to introduce a methyl group at C-14, and the three oxygen functions would be well placed to guide the introduction of the functionality of the aquariolides (Scheme 1). Compound **5** was envisaged as arising from a spirocyclic enone **6** by a ring-expanding Cope rearrangement followed by isomerization of the double bond. A Pauson−Khand reaction of the enyne **7** might give **6**. Although the Pauson−Khand reaction has become a mainstream synthetic tool,[4] it was unclear whether this reaction would proceed efficiently in the sterically congested context of **7**. It was anticipated that **7** could be constructed stereoselectively from

(1) Taglialatela-Scafati, O.; Deo-Jangra, U.; Campbell, M.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2002**, *4*, 4085−4088.

(2) Taglialatela-Scafati, O.; Craig, K. S.; Rebérioux, D.; Roberge, M.; Andersen, R. J. *Eur. J. Org. Chem.* **2003**, 3515−3523.

(3) (a) Look, S. A.; Fenical, W.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 5026−5027. (b) Pordesimo, E. O.; Schmitz, F. J.; Ciereszko, L. S.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1991**, *56*, 2344−2357. (c) Banjoo, D.; Mootoo, B. S.; Ramsewak, R. S.; Sharma, R.; Lough, A. J.; McLean, S.; Reynolds, W. F. *J. Nat. Prod.* **2002**, *65*, 314−318.

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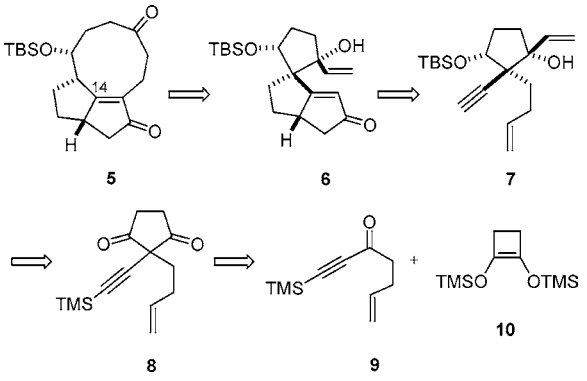
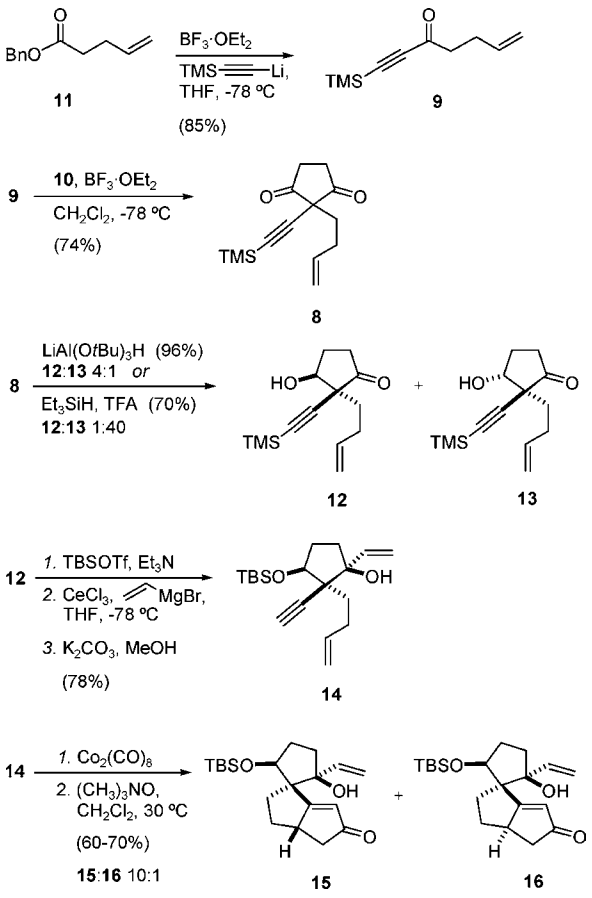
Scheme 1. Retrosynthetic Analysis



1,3-diketone **8** in a few steps. Geminal acylation of known ynone **9** with 1,2-bis[(trimethylsilyl)oxy]cyclobutene **10** would be relied upon to provide **8**.

Starting from benzyl ester **11**, ynone **9** was prepared in 85% yield following the procedure of Yamaguchi[5] (Scheme 2). With use of the methodology developed in our laboratory,[6] the ketone of **9** underwent geminal acylation upon treatment with **10** in the presence of $BF_3{\cdot}OEt_2$ to provide diketone **8**. It was anticipated that addition of a vinyl group to one of the carbonyls of **8** would occur onto the seemingly more accessible, acetylenic face of the five-membered ring, leading to a cis relationship between the vinyl and acetylenic groups. Attempts to install this vinyl group by the addition of a Grignard reagent to **8** were unsuccessful, likely due to the susceptibility of the putative product, a β-hydroxyketone, to undergo retroaldol ring opening. To circumvent this problem, it was decided to reduce one of the ketones of **8** and to protect the resulting alcohol before adding the vinyl group. Again, it was assumed that this reduction would proceed diastereoselectively, and that hydride reagent would be delivered preferentially syn to the alkyne. Protection of the newly formed alcohol would then have the added benefit of further directing addition of a vinyl Grignard reagent by blocking the alkenyl face of the cyclopentanone.

Scheme 2. First Steps, Including Geminal Acylation, Addition of a Vinyl Group, and the Pauson−Khand Reaction



The monoreduction of diketone **8** with $NaBH_4$ gave a 2:1 ratio of diastereomeric alcohols (**12** and **13**). Use of lithium tri(*tert*-butoxy)aluminohydride in THF at −78 °C improved this ratio to 4:1. Monoreduction of **8** with $EtSi_3H$ in TFA[7] had the opposite diastereoselectivity, giving mostly **13** (over 40:1). However, the stereochemistry of the monoalcohols was not known initially because the results of NOE experiments with **12** and **13** were ambiguous. It was decided to proceed first with the major isomer from the lithium tri(*tert*-butoxy)-aluminohydride reduction (**12**). In an efficient sequence, **14** was constructed by TBS protection of the alcohol, addition of vinylmagnesium bromide in the presence of anhydrous $CeCl_3$,[8] and basic methanolysis of the TMS group. It is particularly noteworthy that addition of the vinyl group occurred with complete stereoselectivity. Although, once again, NOE experiments did not lead to an unambiguous assignment of the relative stereochemistry of **14**, an X-ray crystal structure of a later intermediate (**15**) would confirm that both the hydride and the organometallic had added preferentially anti to the acetylenic face of the five-membered ring.

The Pauson−Khand step was evaluated by using **14**. Following protocols for the stoichiometric version of the reaction,[9,10] **14** was treated with $Co_2(CO)_8$ and the resulting complex was subjected to different conditions known to effect cyclization (Table 1). The highest yield and the best diastereoselectivity were obtained by using as the promoter anhydrous trimethylamine *N*-oxide[9] in dichloromethane at 30 °C. The poor yields obtained at lower temperatures suggest that there is a significant activation energy for the successful cyclization of the alkene to the sterically congested

(4) For recent reviews, see: (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (b) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32−42.

(5) Yamaguchi, M.; Shibato, K.; Fujiwara, S.; Hirao, I. *Synthesis* **1986**, 421−422.

(6) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485−1491.

(7) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415−5421.

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(9) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. *Synlett* **1991**, 204−206.

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Table 1. Results for the Pauson−Khand Reaction of the Cobalt Complex of **14**[a]

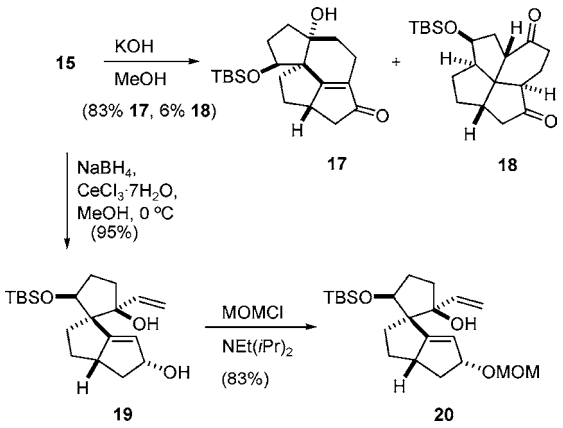
promoter, solvent	temp (°C)	yield (%)	dr **15**:**16**	recovered **14** (%)
thioanisole (3.5 equiv), DCE	83	32	6:1	60
NMO dihydrate (7 equiv), CH_2Cl_2	22	51	7:1	35
TMANO (anhydrous, 8 equiv), CH_2Cl_2	0	22	3:2	68
TMANO (anhydrous, 8 equiv), CH_2Cl_2	30	60−70	10:1	8−12

[a] DCE = dichloroethane, NMO = *N*-methylmorpholine *N*-oxide, TMANO = trimethylamine *N*-oxide.

cobalt center. What is not clear is why poor yields were accompanied by more similar proportions of the two diastereomers, **15** and **16**. The X-ray crystal structure of the major diastereomer **15** confirmed that its OTBS group was positioned on the convex face of the newly formed diquinane.[11]

Although the two olefins in **15** were on opposite sides of the spirocycle, an anionic oxy-Cope rearrangement[12,13] was attempted, nevertheless. This was because there is precedence for reaction pathways via the normally less-favored boatlike transition states.[13,14] Treatment of **15** with either KH in THF or just KOH in methanol resulted in the rapid formation of a tetracyclic enone **17** in 83% yield, accompanied by a small amount of a [5.5.5.6]fenestrane **18** (Scheme 3). X-ray crystal

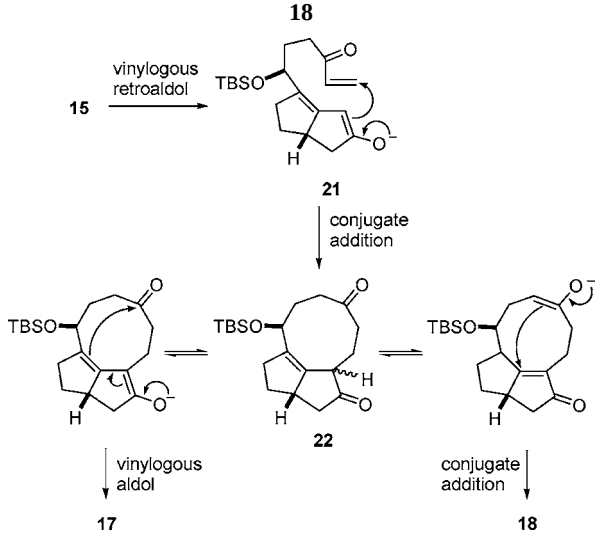
Scheme 3. Attempted Anionic Oxy-Cope Rearrangement with **15**



structures of **17** and **18** confirmed their relative stereochemistries. Aldol processes must have been involved in the formation of the fourth ring of these compounds, but an initial anionic oxy-Cope process could be ruled out in the following way. Reduction of **15** with use of Luche conditions[15] gave a single alcohol **19**, which was protected as the MOM ether **20**. Subjecting **20** to anionic oxy-Cope conditions (KH and 18-crown-6 in hot THF) did not lead to any reaction.

The formation of **17** and **18** must have occurred through a mechanism involving initial deprotonation of the hydroxyl of **15** and subsequent vinylogous retroaldol fragmentation (Scheme 4). Conjugate addition of the resulting enolate **21**

Scheme 4. Suggested Mechanism for the Formation of **17** and **18**



would lead to the nine-membered-ring compound **22** (which would have been the product of a concerted anionic oxy-Cope with **15**). An enolate of the diquinane ketone of **22** must lead to a transannular vinylogous aldol and thus to **17**. On the other hand, an enolate of the ketone on the nine-membered ring of **22** might result in a transannular 1,4-addition and thus to **18**. That **22** was not detected in the product mixture suggests strongly that **22** exists in a conformation in which the opposite sides of its nine-membered ring are exceptionally close.

Compound **17** was used to form the desired ring system in the following way (Scheme 5). The TBS group of **17** was removed and replaced with a mesylate **23**. Reduction of the ketone with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in methanol gave a single alcohol **24**. Grob fragmentation with KO*t*Bu in the presence of 18-crown-6 provided the desired ring system,[16] but in an unacceptable yield. Protection of the hydroxyl group of **24** as a MOM ether **26** and Grob fragmentation of **26** generated the desired ring system **27** in 81% yield.

While the Grob fragmentation strategy (Scheme 5) to construct the medium-sized ring was successful, this ap-

(11) Proposed mechanism of the Pauson−Khand process: Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854.

(12) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

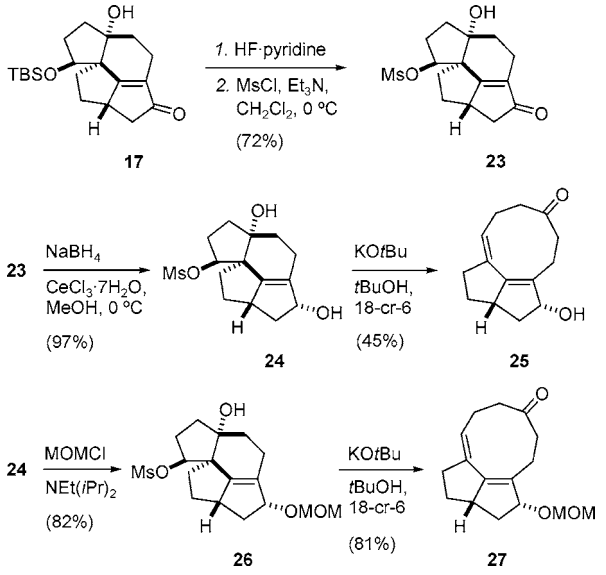
(13) Paquette, L. A. *Tetrahedron* **1997**, *41*, 13971−14020.

(14) Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265−277.

(15) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.

(16) Another example of a Grob fragmentation to produce a nine-membered ring: Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567−1574.

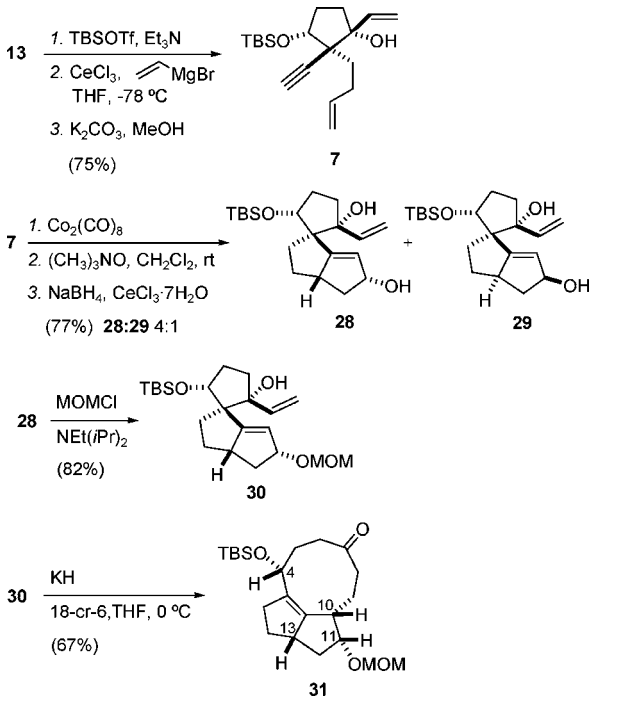
Scheme 5. Aquariane Ring System by Grob Fragmentation



proach lacked much of the aesthetic appeal of the original plan. Keto-alcohol **13**, the product from the reduction of **8** with triethylsilane in TFA, was subjected to a three-step sequence that was similar to what had been employed with **12**. This led to compound **7** exclusively, in which the vinyl group was cis to the alkyne. The implication of this and the corresponding reaction with **12** is that the silyloxy group of **12** or **13**, which is β to the carbonyl, exerts a much greater influence on the stereoselectivity of the vinyl addition than does the carbon substitution α to the carbonyl.

When **7** was complexed with $Co_2(CO)_8$ and treated with trimethylamine *N*-oxide, the Pauson−Khand reaction proceeded well to give a 4:1 ratio of inseparable diastereomers. Reduction of these enones with Luche conditions[15] gave alcohols **28** and **29** (in a ratio of roughly 4:1 by NMR), which were separated by column chromatography. Protection of the major alcohol **28** as a MOM ether gave **30**. NOE experiments revealed the proximity of hydrogens on the vinyl group and the hydrogen on the annular olefin, establishing the likelihood of a favorable geometry for an anionic oxy-Cope process. As expected, subjecting **30** to appropriately basic conditions smoothly provided ketone **31**. NOE experiments showed that the hydrogens on C-4, C-10, C-11, and C-13 (aquariane numbering) were all cis to each other, thus establishing the relative stereochemistry of **31**.

Scheme 6. Aquariane Ring System by an Anionic Oxy-Cope Rearrangement



In summary, viable routes to the ring system of the aquariolide diterpenes have been established. Efforts are underway to adapt the latter route for more elaborate compounds related to aquariolides.

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Supporting Information Available: Experimental procedures and characterization data, ^1H and ^{13}C NMR spectra, and X-ray crystallographic data for compounds **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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