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Total Synthesis of Muamvatin

Dale E. Ward* and M. Mehdi Zahedi

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon SK S7N 5C9, Canada

dale.ward@usask.ca

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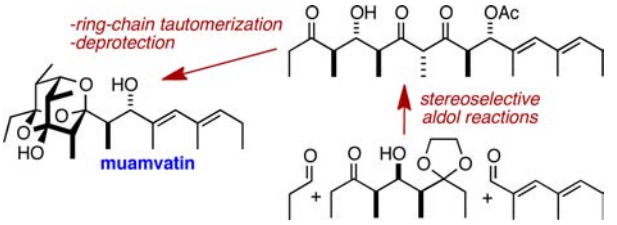
ABSTRACT



Enantioselective total synthesis of muamvatin was achieved by ring-chain tautomerization of an acyclic derivative assembled by sequential substrate-controlled stereoselective aldol reactions of a chiral ketone with two achiral aldehydes. Although the trioxaadamantane tautomer was shown to be thermodynamically more stable than alternative forms, the kinetic barrier to cyclization was significant. This observation raises doubts about the proposed formation of muamvatin as an artifact of isolation.

Pulmonate mollusks of genus *Siphonaria*, also known as false limpets, are primative air-breathing herbivores that reside in intertidal zones along rocky coastlines in temperate and subtropical regions.[1] Siphonariid mollusks are a rich source of polypropionates, apparently originating via *de novo* biosynthesis; however, the role of these compounds in the chemical ecology of the organisms is poorly understood.[2] This issue is complicated because of uncertainty on whether the reported structures are biosynthetic products or artifacts of isolation.[3] An avenue to explore this question involves examining the properties of putative 'acyclic' precursors prepared by total synthesis.[4] In this paper we report the synthesis of muamvatin (**1**) via this strategy.

Muamvatin (**1**) is an extraordinary octapropionate isolated from *Siphonaria normalis* by Ireland et al. (Scheme 1).[5] Synthetic studies by Hoffmann and Dahmann[6] and the total synthesis by Paterson and Perkins[7] confirmed the proposed structure and established the relative configurations at C-10 and C-11 and the absolute configuration of **1**. The so-called 'trioxaadamantane' ring system present in **1** is highly unusual and has been found in only one other 'natural product', caloundrin B (**2**).[8] Formally, this ring system is a ring-chain tautomer of a 5-hydroxy-3,7,9-trione and synthetic studies[6,7,9] have shown that this functional group array is sensitive to both acid and base. En route to **1**, the trioxaadamantane **4** was prepared by exposure of **8** to silica gel, leading the authors to hypothesize that **1** might be formed from **3** (or equivalent) under thermodynamic control during the isolation process.[7] Subsequently, MM2 calculations suggested that **1** was considerably more stable than alternative hemiacetal or spiroacetal forms.[10]

To test the hypothesis that **1** might be formed as an isolation artifact, we sought to prepare the putative precursor **3**. Retrosynthetic analysis (Scheme 1) suggested a plan based on sequential aldol reactions of a chiral

(1) Hodgson, A. N. *Oceanogr. Mar. Biol.* **1999**, *37*, 245–314.
(2) (a) Darias, J.; Cueto, M.; Diaz-Marrero, A. R. *Prog. Mol. Subcell. Biol.* **2006**, *43*, 105–131. (b) Garson, M. J. *Prog. Mol. Subcell. Biol.* **2006**, *43*, 159–174.
(3) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477–493.
(4) (a) Beye, G. E.; Ward, D. E. *J. Am. Chem. Soc.* **2010**, *132*, 7210–7215. (b) Becerril-Jiménez, F.; Ward, D. E. *Org. Lett.* **2012**, *14*, 1648–1651.
(5) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680–6682.
(6) (a) Hoffmann, R. W.; Dahmann, G. *Tetrahedron Lett.* **1993**, *34*, 1115–1118. (b) Dahmann, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1994**, 837–845. (c) Hoffmann, R. W.; Dahmann, G. *Chem. Ber.* **1994**, *127*, 1317–1322.
(7) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610.
(8) Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994**, *47*, 2255–2269.
(9) Beye, G. E.; Goodman, J. M.; Ward, D. E. *Org. Lett.* **2009**, *11*, 1373–1376.
(10) Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929–6932.

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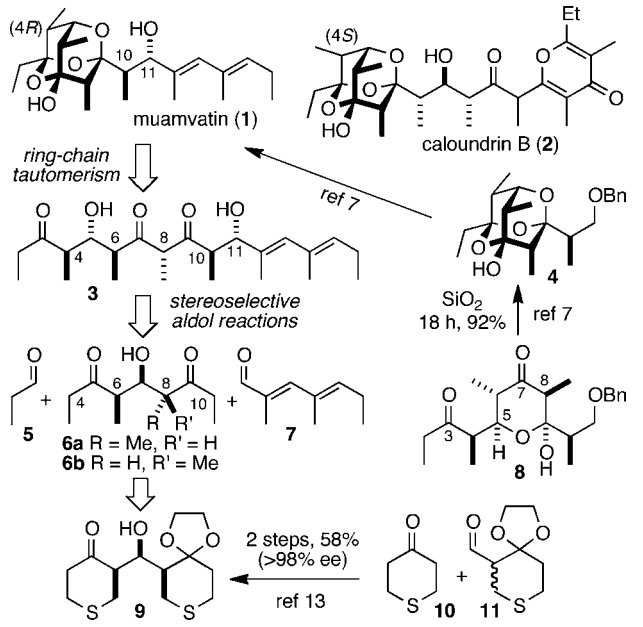
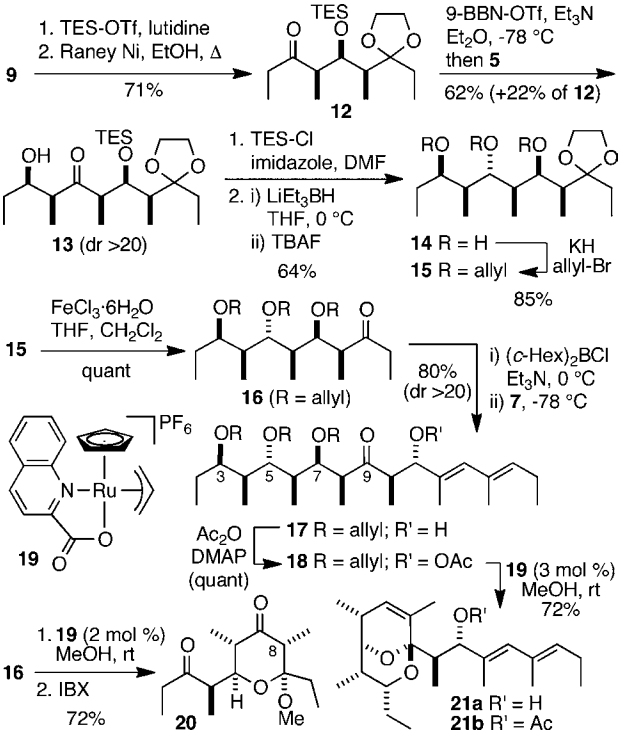
Scheme 1. Retrosynthetic Analysis of Muamvatin (**1**)



derivative of dione **6** with the achiral aldehydes **5** and **7** with substrate-controlled stereoselectivity. In reactions of achiral aldehydes with chiral ethyl ketones related to **6**, the diastereoface selectivity of the derived boron or Ti(IV) enolates is controlled by the configuration of the α-methyl stereocenter predominantly leading to aldol adducts with α,α′-*syn* relative configuration with the relative topicity (α′,β′-*syn*/*anti*) dictated by the enolate configuration.[11] Thus, addition of **5** to the enolate from the C-5 ketone in **6** should give an adduct with the desired 4,6-*syn* relative configuration. However, because aldol reactions of related chiral ethyl ketones rarely produce α,α′-*anti*-α′,β′-*anti* adducts,[12] achieving the 8,10-*anti*-10,11-*anti* relative configuration present in **3** via an aldol reaction of a derivative of **6a** with **7** is doubtful. This problem can be resolved by considering that the C-8 configuration in **3** is labile and that transformation to muamvatin (**1**) would set the required configuration under thermodynamic control.[10] Thus, **6b** becomes a plausible synthon and reaction of its (*E*)-enolborinate (derived from the C-9 ketone) with **7** should establish the desired relative and absolute configurations for C-10 and C-11.[11b] In principle, the configuration at C-7 in **6b** has little influence on the above discussion; however, ease of synthesis strongly favors the *syn*-*syn* diastereomer, and the readily available[13] **9** was selected as the reagent equivalent to **6b**.

The synthesis commenced with protection of the hydroxyl group in **9** as the corresponding triethylsilyl (TES) ether followed by Raney Ni desulfurization to provide ketone **12** (Scheme 2). Reaction of **5** with the (*Z*)-enol borinate derived from **12** gave the expected adduct **13** with excellent stereoselectivity.[14] We were unable to obtain the required *anti* diol by reduction of **13**; however, reaction of the bis(TES ether) derivative with $LiEt_3BH$ (dr 7) followed by removal of the silyl groups produced the desired triol **14**. Conversion of **14** to the tris(allyl ether) **15** and $FeCl_3$-mediated[15] hydrolysis of the ethylene acetal afforded ketone **16**. Addition of the known[6b] **7** to the (*E*)-enol dicyclohexylborinate prepared from **16** selectively gave **17**, completing the carbon skeleton of 8-*epi*-**3** with all stereocenters in place.

Scheme 2. Assembly of the Carbon Skeleton of **3**



Conversion of **17** to 8-*epi*-**3** would require chemoselective oxidation at C-3 and C-7. In analogy with Paterson's synthesis of **8**,[7] we expected that the product from deallylation of **17** would exist as the hemiacetal tautomer thereby protecting the C-5 hydroxy group from oxidation. To test the feasibility of that plan, ketone **16** was treated with Kitamura's catalyst (**19**)[16] in MeOH and the crude product was subjected to IBX oxidation affording the tetrahydropyrone **20** in good yield (Scheme 2). Surprisingly, when **17** or its acetate derivative **18** was similarly exposed to **19**, only the bicyclic acetal **21a** or **21b**, respectively, was

(11) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142. (c) Duffy, J. L.; Yoon, T. P.; Evans, D. A. *Tetrahedron Lett.* **1995**, *36*, 9245–9248.

(12) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **2001**, *66*, 2747–2756.

(13) (a) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, H. M.; Karagiannis, A.; Becerril-Jimenez, F. *Synlett* **2011**, 508–512. (b) Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989–8992.

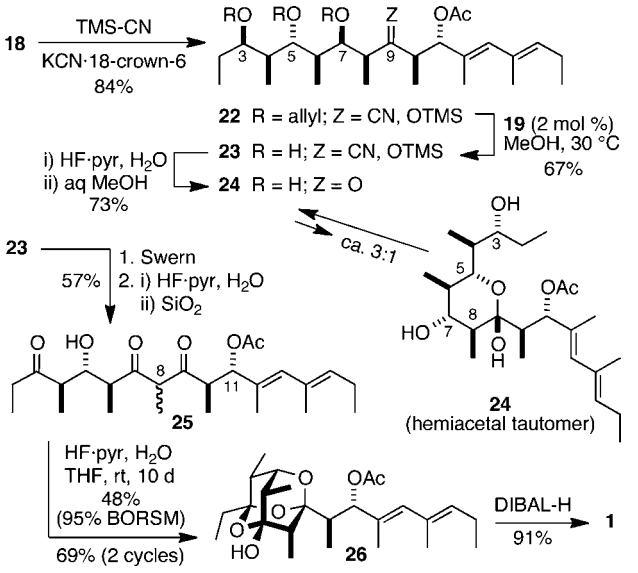
(14) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229–1232.

(15) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686.

(16) (a) Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* **2004**, *6*, 1873–1875. (b) Tanaka, S.; Saburi, H.; Kitamura, M. *Adv. Synth. Catal.* **2006**, *348*, 375–378.

obtained. Formation of **21** requires elimination of the C-7 *O*-allyl group (or OH group in the deallylated intermediate) in **17** or **18**, and this reaction could not be suppressed despite considerable experimentation.

Scheme 3. Synthesis of Muamvatin (**1**)



Reasoning that the undesired elimination of the C-7 oxygen substituent was facilitated by the C-9 carbonyl group, we prepared the TMS-cyanohydrin derivative **22** as a 1.4:1 mixture of diastereomers by reaction of **18** with TMS-CN and KCN·18-crown-6 (Scheme 3).[17] Gratifyingly, treatment of **22** with **19** in MeOH smoothly produced the triol **23**. It is noteworthy that **19** was able to remove the allyl groups in **22** without isomerizing the diene or affecting the dienyl acetate. Unfortunately, the cyclic hemiacetal of the corresponding ketone **24** was the minor tautomer, thereby preventing application of Paterson's strategy for chemoselective oxidation of the C-3 and C-7 hydroxy groups. Alternatively, we explored the relative reactivity of the hydroxy groups in **23** and found that the 3,7-bis-*O*-TES derivative was formed selectively on reaction with excess TES-OTf in the presence of 2,6-lutidine. Accordingly, Swern oxidation of **23** achieved the desired chemoselective oxidation at C-3 and C-7 and **25** was obtained in good yield after hydrolysis of the TMS ether and removal of the cyanohydrin. Careful analysis of the ^{1}H and ^{13}C NMR spectra of **25** in $CDCl_3$ suggested the presence of a 1:2:2 mixture of enol (δ_H 16.97; δ_C 199.1, 193.6, 105.0) and two β-diketo tautomers ($\delta_{HC\text{-}8}$ 4.02 (q), 4.01 (q); $\delta_{C\text{-}8}$ 61.8, 59.8), respectively (ca. 85%), along with ca. 7% of hemiacetal (OH at δ_H 4.99). The small amount of hemiacetal tautomer(s) present was unexpected in light of studies[4,6,7] on related compounds and considering the presence of both C-8 diastereomers of the β-diketo form.[18]

We have previously shown that imidazole is an excellent catalyst to promote keto–enol and ring-chain tautomerism in sensitive substrates.[4,9,19] Remarkably, exposure of **25** to imidazole (1 M in $CDCl_3$, 40 °C, 5 days) did not lead to **26**. Compared to starting material, the recovered **25** had a larger proportion of the hemiacetal tautomer (to ca. 50%) and a different ratio of the C-8 diastereomers of the β-diketo form (to ca. 2:1), perhaps representing the equilibrium ratio. In contrast, reaction of **25** with HF·pyridine, pyridine, and water in THF solution[6,9] slowly produced **26** (45–50% in 10 d) and resubjecting the recovered **25** (45–50%)[20] to the same conditions provided additional **26** (35–40%) (Scheme 3). Subjecting **26** to imidazole or HF·pyridine under the same conditions as above gave no evidence for the formation of an 'acyclic' or hemiacetal tautomer suggesting the trioxaadamantane is considerably more stable than alternative tautomers.[10] Finally, reduction of **26** with DIBAL-H gave muamvatin (**1**) in excellent yield. Spectroscopic data (^{1}H and ^{13}C NMR, MS) for synthetic **1** ($[\alpha]_D$ +60; *c* 0.13, CH_2Cl_2) were fully consistent with those reported[5] for 'natural' **1** ($[\alpha]_D$ +61.1; *c* 0.175, CH_2Cl_2).[21]

Muamvatin (**1**) was unchanged on treatment with imidazole or HF·pyridine as above demonstrating its expected thermodynamic stability relative to alternative tautomers.[10] What of the origin of **1**? Synthetic studies on caloundrin B (**2**) strongly suggest that formation of its (unstable) trioxaadamantane ring system is enzyme mediated.[4b] Similarly, the significant kinetic barrier observed for the formation of **26** from **25** implies that a similar process is unlikely to occur during isolation. Because of the possibility that a C-11 hydroxyl group (cf. **3**) might accelerate the formation of the trioxaadamantane, considerable effort was made to prepare **3** and/or 8-*epi*-**3** via this route. Unfortunately, attempted hydrolyses of the acetates in **23** [$La(OTf)_3$/NaOMe][22] and **25** (lipases from *Aspergillis niger*, *Candida rugosa*, and *Pseudomonas cepacia*)[23] failed and attempts to replicate the synthesis with alternative R′ protecting groups (e.g., TES, TBS, TIPS, 4-OTES-butanoyl[24]) on **17** failed to reach the corresponding analogue of **23**.

In conclusion, the enantioselective total synthesis of muamvatin (**1**) was achieved in 15 linear steps from (+)-**9**. The key features of the synthesis involved the following: (*i*) substrate-controlled introduction of all stereocenters (C-4,5,8,10,11); (*ii*) the first demonstration of the use and removal of allyl ether protecting groups on noncarbohydrate[25] sensitive substrates

(17) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822–5823.

(18) For related examples where the 5-hydroxy-1,3-dione tautomer predominated over the alternative hemiacetal, see: Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827–1830.

(19) Ward, D. E.; Sales, M.; Sasmal, P. K. *J. Org. Chem.* **2004**, *69*, 4808–4815.

(20) The recovered **25** had an 'equilibrium' ratio of tautomers similar to that observed after treatment with imidazole.

(21) See the Supporting Information for a detailed comparison of the NMR data.

(22) (a) Neverov, A. A.; McDonald, T.; Gibson, G.; Brown, R. S. *Can. J. Chem.* **2001**, *79*, 1704–1710. (b) Di Stefano, S.; Leonelli, F.; Garofalo, B.; Mandolini, L.; Bettolo, R. M.; Migneco, L. M. *Org. Lett.* **2002**, *4*, 2783–2785.

(23) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*.; Pergamon: Oxford, U.K., 1994.

(24) Renton, P.; Gala, D.; Lee, G. M. *Tetrahedron Lett.* **2001**, *42*, 7141–7143.

under very mild conditions using Kitamura's catalyst (**19**); (*iii*) chemoselective Swern oxidation of a 1,3,5-triol to obtain a 3-hydroxy-1,5-dione. Although **26** is thermodynamically more stable than alternative tautomers, the kinetic barrier to cyclization is also significant. Consequently, the demonstrated thermodynamic stability of muamvatin (**1**) is not sufficient to conclude that it is formed as an isolation artifact. Thus, similar to caloundrin B (**2**), muamvatin (**1**) must be considered a plausible biosynthetic product; however, further research is required to settle this question.

(25) Liu, X. Y.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638–3648.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all reported compounds; comparison of NMR data for natural and synthetic material; structure determination for **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.