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On the Origin of Siphonariid Polypropionates: Total Synthesis of Caloundrin B and Its Isomerization to Siphonarin B

Fabiola Becerril-Jiménez and Dale E. Ward*

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

dale.ward@usask.ca

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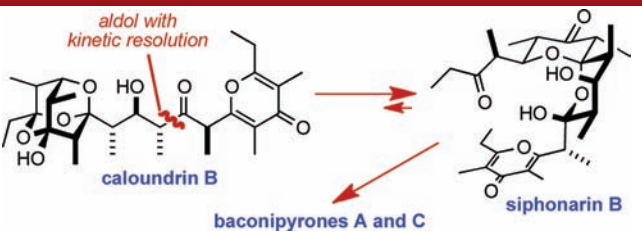
ABSTRACT



Enantioselective synthesis of the enantiomer of caloundrin B was achieved by strategic aldol coupling of an enantiopure trioxaadamantane-containing ketone with a racemic pyrone-containing aldehyde via kinetic resolution. In the presence of imidazole, *ent*-caloundrin B is cleanly isomerized to *ent*-siphonarin B confirming the proposed structure and absolute configuration for caloundrin B and establishing that it is a plausible biosynthetic product from which siphonarin B and baconipyrones A and C can originate.

Caloundrin B (**2**),[1] siphonarin B (**3**),[2] baconipyrone A (**4**),[3] and baconipyrone C (**5**)[3] are γ-pyrone containing decapropionates isolated from extracts of the pulmonate mollusk (false limpet) *Siphonaria zelandica*.[4] The structural diversity represented in **2**–**5** has been postulated to originate from a common precursor (e.g., **1**) via alternative cyclization/rearrangement cascades possibly orchestrated by the labile configuration at C-8 and perhaps occurring during isolation (Scheme 1).[5] To test that hypothesis, we prepared **1** by total synthesis and demonstrated its isomerization to **3** (70%) under thermodynamic control.[6] A mixture of **4** and **5** was obtained from **3** by retro-Claisen fragmentation of the C8–C9 bond in the presence of alumina.[6] Similar treatment of **1** also gave **4** and **5**; however, the major product was a new structural isomer arising from a different retro-Claisen pathway (i.e., cleavage at C7–C8). Those observations suggested that **4** and **5** were plausible isolation artifacts derived from **3** (but not **1**). However, the origin of **2** was a missing piece of the puzzle as we were unable to detect its presence in attempts to induce isomerization of **1** or **3** under a variety of conditions. Consequently, we speculated that **2** was either thermodynamically unstable relative to **1** and **3**,[7] the kinetic barrier for its formation was high, or the proposed

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(7) MM2 calculations have suggested that **2** is ca. 13 kJ/mol less stable than **3** (ref 5a).

(8) The relative configuration for the trioxaadamantane motif in **2** was established by extensive analysis of NMR spectra; however, the proposed relative configuration for C10–C14 and the absolute configuration for **2** were assigned based on the presumed relationship with its cometabolite **3** (see ref 1). The sample decomposed to unknown products during the NMR studies, and additional **2** has apparently not been isolated.

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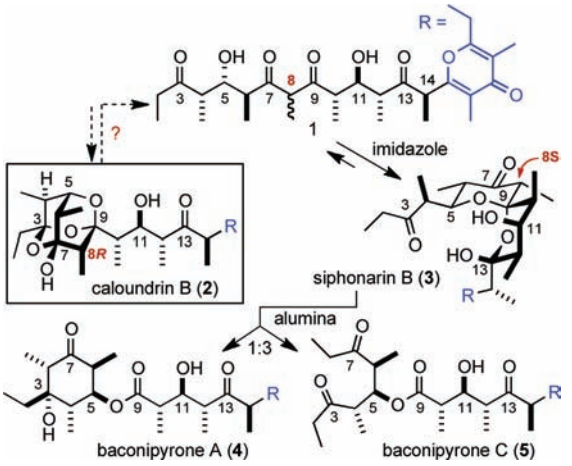
structure was incorrect.[6,8] In this paper, we report the total synthesis of *ent*-**2** and its facile isomerization to *ent*-**3**. These results fully corroborate the proposed structure for **2** and imply that it is unlikely to be an isolation artifact.

Scheme 1. Siphonariid Decapropionates



The anticipated[7,8] instability of **2**, corroborated by our failed attempts at the synthesis of **2** by isomerization of **1** or **3**,[6] predicated a synthetic plan based on elaboration of a preformed 2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (hereafter "trioxaadamantane") fragment (Scheme 2). We chose to assemble the carbon framework of **2** by aldol coupling of **7** with **8**.[9] Although both enantiomers of **8** are known,[10] the syntheses are lengthy and the product is unstable and prone to racemization. We prepared (±)-**8** from the readily available **6**[11] by treatment of its NaN(SiMe$_3$)$_2$ generated anion[12] with formaldehyde followed by oxidation with 2-iodoxybenzoic acid (IBX). Model studies[13] indicated that aldol reactions of (±)-**8** with Li and B enolates of 3-pentanone were highly Felkin selective suggesting that kinetic resolution would be possible in analogous reactions with suitable enantiopure ketones (e.g., **7**).[14] The possibility of selectively obtaining different adduct diastereomers simply by altering the reaction conditions was seen as an advantage of this synthetic approach,[14] especially if the proposed relative configuration of **2** was incorrect.[8] Formally, the trioxaadamantane ring system is a ring−chain tautomer of a 3-hydroxy-1,5,7-trione and all reported syntheses of this acid- and base-sensitive ring system have relied on a favorable equilibrium with ring-opened tautomers established under mild conditions.[15] In the context of synthetic studies on muamvatin (**15**), both **14**[15a] and *ent*-10-*epi*-**14**[15b] were prepared in moderate to excellent yields under thermodynamic control. Although formation of the caloundrin B ring system is more challenging,[16] we selected the (4*S*,10*S*) diastereomer **12** as the core trioxaadamantane fragment with hopes that it would be a stable tautomer of **13**. The thiopyran route to polypropionates[17] was expected to provide stereoselective access to **13** from the known precursors **9**,[18] **10**,[19] and **11**.[20] Ketone **7** would be available from **12** by straightforward functional group manipulation.

The synthesis commenced with desulfurization of **16** (>98% ee), prepared in two steps from **9** and **10**,[14,18] followed by aldol reaction of the resulting ethyl ketone via its Li enolate with **11**[20] to afford **17** as a mixture of diastereomers in good yield (Scheme 3). Hydrolysis of the ethylene acetal and silyl ether in **17** followed by chemoselective oxidation of the C-9 alcohol with the Dess-Martin periodinane (DMP) and equilibration of the 3-hydroxy-1,5,7-trione product in the presence of imidazole provided the hemiacetal **19** in moderate yield. Despite extensive experimentation, we were unable to obtain the desired **12** by tautomerization of **19**.[21] We speculated that **19** might be favored in the equilibrium because of a stabilizing intramolecular hydrogen bond between the anomeric OH group and the benzyl (Bn) ether. The juxtaposition of these groups is enforced by avoidance of a *syn*-pentane interaction between the C-8 Me group and the substituents at C-10. The C-10 epimer of **19** should not be similarly stabilized, and to test that hypothesis, a mixture of adducts **18** was prepared by desulfurization of *ent*-**16** followed by aldol reaction with **11** as described above. Gratifyingly, subjecting **18** to the same three-step sequence that gave **19** from **17** produced a separable 3:1 equilibrium mixture of trioxaadamantane **20** and the corresponding hemiacetal (i.e., *ent*-10-*epi*-**19**).[22]

(9) Formation of the C11−C12 bond by aldol coupling was rejected because of anticipated difficulties in forming an enolate in the presence of the pyrone and in achieving the required stereoselectivity.

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(13) Details of this study will be reported separately.

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(16) Computational comparison (ref 15e) of truncated models (i.e., with an Et substituent at C-9) of the caloundrin B trioxaadamantane (4*R*,8*R* relative configuration) and muamvatin trioxaadamantane (4*S*,8*R* relative configuration) suggests the former is 2 kJ/mol less stable and the equilibrium for its formation 5 kJ/mol less favorable.

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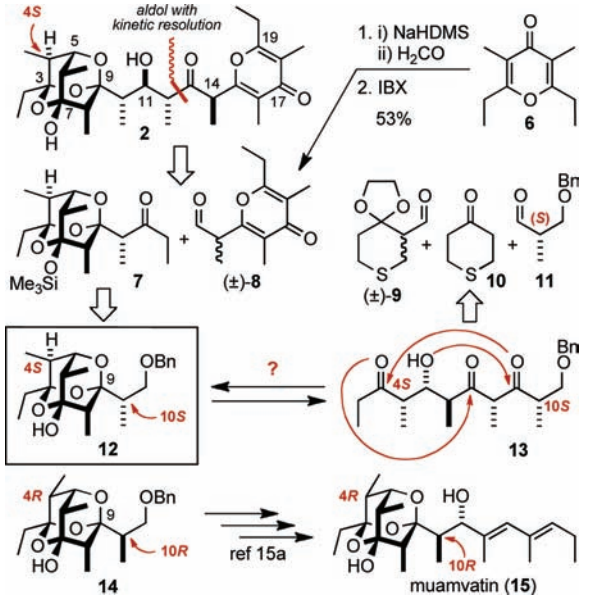
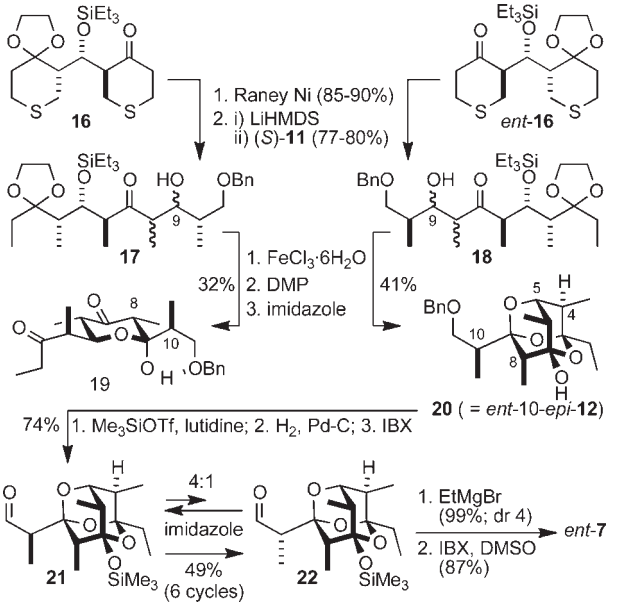
(21) The anomer of **19** is the direct precursor of **12**. See ref 15e for reaction conditions used for isomerization.

(22) The relative configuration for the trioxaadamantane in **20** was confirmed by NMR ($CDCl_3$) as described in ref 15e; $\delta_{C\text{-}6}$ = 35.8, $\delta_{C\text{-}8}$ = 34.9, $\delta_{H3CC\text{-}6}$ = 0.89, $^3J_{HC4-HC5}$ = 3.5 Hz, and $^3J_{HC6-HC8} \approx 0$ Hz are particularly diagnostic. The absolute configuration of the trioxaadamantane is established by the absolute configuration of the known **16**. The (*S*) configuration at C-10 originates from the known (*S*)-**11**; isomerization can be ruled out because *ent*-**20** was not formed from **17** and *ent*-**19** was not formed from **18**.

Scheme 2. Retrosynthetic Analysis of Caloundrin B (**2**)



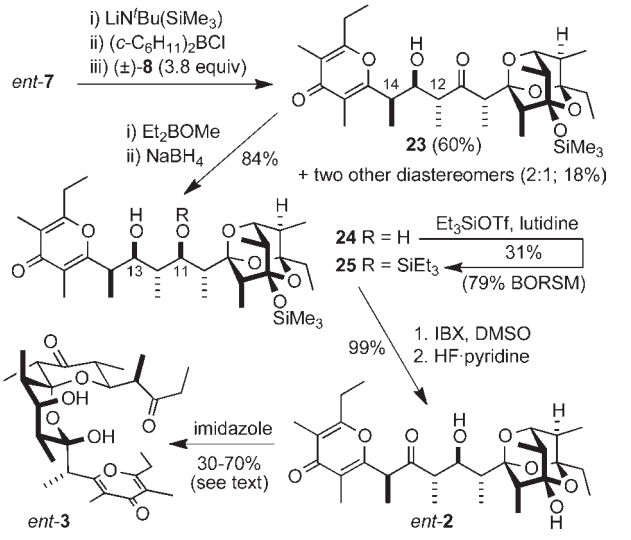
Scheme 3. Synthesis of *ent*-**7**



Our inability to prepare a trioxaadamantane with the desired relative configuration (e.g., **12**) under thermodynamic control prompted consideration of routes involving modification of stable analogues. In that regard, previous studies showed that protection of the trioxaadamantane hemiacetal OH group as its trimethylsilyl (TMS) ether resulted in a much more stable ring system that could be deprotected under mild conditions.[15e] Eventually we settled on a rather lengthy but efficient isomerization sequence to correct the relative configuration at C-10 in **20** (Scheme 3). After 'locking' the trioxaadamantane in **20** as its TMS ether, the benzyl ether was hydrogenolyzed and the resulting alcohol was oxidized with 2-iodoxybenzoic acid (IBX) to afford aldehyde **21**. Treatment of **21** with imidazole in $CHCl_3$ gave a separable 4:1 equilibrium mixture of **21** and **22**, respectively. After six cycles of equilibration, **22** (dr 17) was obtained in 49% yield along with recovered **21** (28%; dr 17). The desired *ent*-**7** was easily obtained from **22** by treatment with EtMgBr followed by IBX oxidation of the resulting alcohol.

To obtain the relative configuration present in **2** from *ent*-**7** requires stereoselective aldol reaction with (*S*)-**8** (Scheme 4). Considering the high Felkin selectivity observed[13] for aldol additions of 3-pentanone to **8** and the propensity for (*E*)-boron enolates of chiral ethyl ketones bearing an α-methyl substituent to give aldol adducts with *anti* relative topicity and 1,3-*syn* methyl groups,[23] application of the multiplicativity rule[24] suggests that reaction of the (*E*)-boron enolate of *ent*-**7** with (±)-**8** should selectively give **23** via preferential reaction with (*S*)-**8**.[14] In the event, attempted formation of the boron enolate by reaction of *ent*-**7** with (*c*-C_6H_{11})$_2$BCl and Et_3N led to aldol adducts with very low conversion. However, reaction of *ent*-**7** with LiN^tBu(SiMe_3)[25] followed by treatment of the resulting putative (*E*)-Li enolate with (*c*-C_6H_{11})$_2$BCl and then (±)-**8** (3.8 equiv) produced the desired **23** (60%) along with a 2:1 mixture of two (of the seven possible) other diastereomers (18%).[26] Comparison of the ^{13}C NMR spectrum of **23** with those of model compounds indicated a 12,13-*anti*-13,14-*syn* relative configuration as shown;[13] however, the 10,12-*syn* relative configuration was presumed based on literature precedent.[23]

Scheme 4. Synthesis of *ent*-**2** and Its Isomerization to *ent*-**3**



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Diastereoselective reduction[27] of **23** directed by the OH group at C-13 gave diol **24** (dr > 20) (Scheme 4). Reaction of **24** with $Et_3SiOSO_2CF_3$ led to selective protection of the of the C-11 OH group; however, because any 11,13-bis-(silyloxy) byproduct could not be recycled, it was most efficient to run the reaction to < 50% conversion. IBX oxidation of the resulting **25** followed by treatment with HF·pyridine gave *ent*-**2** in near-quantitative yield. Spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) for *ent*-**2** ($[\alpha]_D$ +50; *c* 0.2, $CHCl_3$) were fully consistent with those reported[1] for **2** ($[\alpha]_D$ −19; *c* 0.16, $CHCl_3$).

To explore the thermodynamic stability and isomerization of caloundrin B, *ent*-**2** was treated with imidazole in $CDCl_3$ at room temperature.[28] After 24 h, a mixture of *ent*-**2**, *ent*-**3** (50% isolated), and *ent*-**1** (mixture of hemiacetals)[6] was obtained. Prolonged reaction (5.5 d) led to complete consumption of *ent*-**2** and produced *ent*-**5** (20% isolated) and *ent*-14-*epi*-**5**[6] along with *ent*-**3** (30% isolated), *ent*-**1**, and other unidentified components. A similar experiment conducted in acetonitrile was monitored by HPLC. After 8 days, a relatively clean transformation to *ent*-**3** (ca.70%) and *ent*-**1** (mixture of hemiacetals)[6] was observed with no more than traces of *ent*-**2** remaining. Spectroscopic data (^{1}H and ^{13}C NMR) for *ent*-**3** ($[\alpha]_D$ −50; *c* 0.1, $CHCl_3$) were fully consistent with those reported[2a] for **3** ($[\alpha]_D$ +13.2; *c* 0.01361, $CHCl_3$). The isolation of *ent*-**3** from these experiments clearly establishes that **2** and **3** share the same absolute configurations at all stereocenters (except C-8) and confirms the proposed relative and absolute configuration for **2**. In addition, these results firmly establish that caloundrin B (**2**) is thermodynamically much less stable than siphonarin B (**3**) (and **1**) confirming previous calculations[7] and explaining our failure[6] to produce **2** by isomerization of **3** (or **1**). Consequently, **2** cannot be an isolation artifact of **1** or **3** but presumably is formed in an enzyme-mediated process. Accordingly, **2** must now be considered as a plausible biosynthetic product from which the formation of **3**–**5** can be readily explained.[6]

In conclusion, the enantioselective total synthesis of *ent*-caloundrin B was achieved in 18 linear steps from (±)-**9**. The key features of the synthesis involved the following: (*i*) synthesis of the challenging trioxaadamantane fragment *ent*-**7** by isomerization of a 10-*epi* derivative formed under thermodynamic control; (*ii*) assembly of the carbon skeleton by a novel aldol reaction of (±)-**8** and *ent*-**7** via kinetic resolution with formation of the required (*E*)-boron enolate by borylation of the corresponding Li enolate. Isomerization of *ent*-**2** into *ent*-**3** confirms the proposed relative and absolute configuration of **2** and establishes that **2** is not an isolation artifact but is a probable biosynthetic product.

Acknowledgment. We thank C. K. (Leon) Lai and M. Mehdi Zahedi (University of Saskatchewan) for preparation of (±)-**8** and *ent*-**16**, respectively, and Prof. Mary Garson (University of Queensland) for providing copies of NMR spectra for caloundrin B. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

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; ^{1}H NMR and HPLC data for isomerization of *ent*-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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