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Synthetic Studies on Siphonariid Polypropionates: Synthesis and Isomerization of the Caloundrin B Trioxaadamantane Ring System

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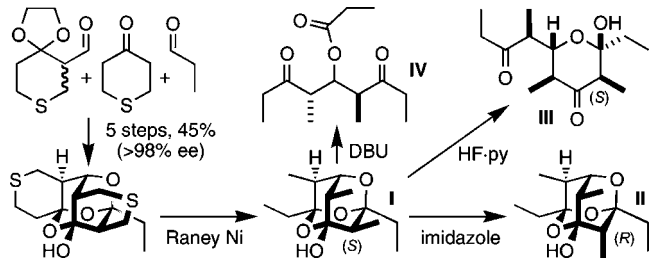
ABSTRACT



(1*R*,3*R*,5*R*,7*R*,8*S*,9*R*,10*S*)-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol (II), a model of the trioxaadamantane ring system embedded in caloundrin B, was prepared by isomerization of the thermodynamically unstable (9*S*)-diastereomer (I) in the presence of imidazole. Alternatively, isomerization of I with HF·py or DBU gave the hemiacetal III or its retro-Claisen ester IV, respectively, which represent structural motifs present in the closely related siphonariid polypropionates siphonarin B and baconipyrone C.

A plethora of structurally diverse marine polypropionates has been isolated from the Mollusca.[1] In many of these polypropionates, several carbons originating from C_1 of propionate retain the ketone oxidation state facilitating formation of various cyclic motifs.[2] The natural product status of such structures has been questioned based on the hypothesis that they are formed via nonenzymatic processes on unstable acyclic biosynthetic products; however, there is little direct experimental evidence of this relationship.[1] For example, siphonarin B (**1**),[3] caloundrin B (**2**),[4] and baconipyrone C (**3**)[5] are closely related polypropionates isolated from siphonariid mollusks (Figure 1). These structures are proposed to arise from alternative cyclization modes of a 5-hydroxy-3,7,9,13-tetraone (e.g., **5**), and some or all may be artifacts of isolation.[1,6] It has been suggested that the cyclization

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(1) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477–493.

(2) For example: 4-pyrones from 1,3,5-triones, dihydro-4-pyrones, and tetrahydro-2-hydroxypyrones from 5-hydroxy-1,3-diones, spiro-bis-acetals from 9-hydroxy-1,5-diones, etc. See also: Socorro, I. M.; Taylor, K.; Goodman, J. M. *Org. Lett.* **2005**, *7*, 3541–3544.

(3) Isolation: (a) Hochlowski, J.; Coll, J.; Faulkner, D. J.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748–6750. (b) Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497–2502. Structure: (c) Garson, M. J.; Jones, D. D.; Small, C. J.; Liang, J.; Clardy, J. *Tetrahedron Lett.* **1994**, *35*, 6921–6924. (d) Paterson, I.; Franklin, A. S. *Tetrahedron Lett.* **1994**, *35*, 6925–6928. Synthesis: (e) Paterson, I.; Chen, D. Y.-K.; Franklin, A. S. *Org. Lett.* **2002**, *4*, 391–394.

(4) Isolation and structure: Blanchfield, J. T.; Brecknell, D. J.; Brereton, I. M.; Garson, M. J.; Jones, D. D. *Aust. J. Chem.* **1994**, *47*, 2255–2269.

(5) Isolation and structure: (a) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371–5374. See also ref 3b. Synthesis: (b) Paterson, I.; Chen, D. Y.-K.; Acena, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513–1516. (c) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864. (d) Yadav, J. S.; Sathaiah, K.; Srinivas, R. *Tetrahedron* **2008**, DOI: 10.1016/j.tet.2008.12.049.

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cascades leading to **1** and **2** are thermodynamically driven and controlled by the configuration at C-8, a center that could be readily epimerized in the putative acyclic precursor **5**.[4,6] In light of the above results, it is surprising that there is only a single report of the isolation of **2** whereas **1** has been isolated several times.[3−5] In an effort to address the proposed relationships among **1**−**3** experimentally, we have been working toward the total synthesis of **2**. Herein, we report the synthesis and isomerization of the 2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol ring system (hereafter "trioxaadamantane") contained in caloundrin B (**2**).

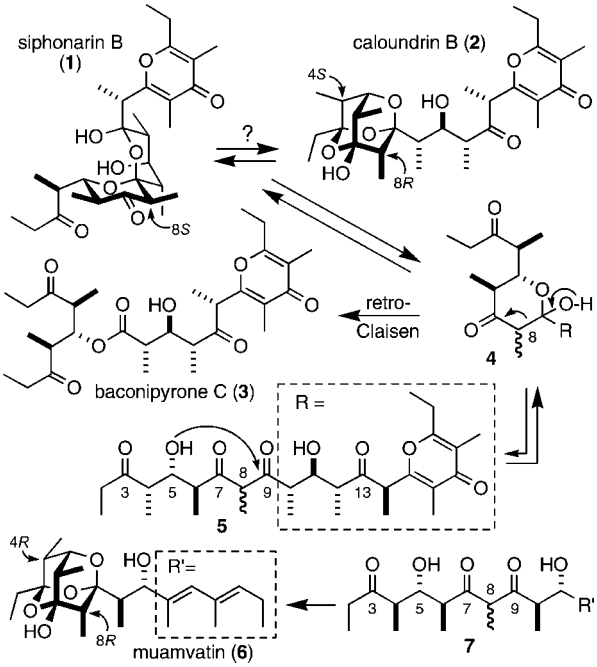
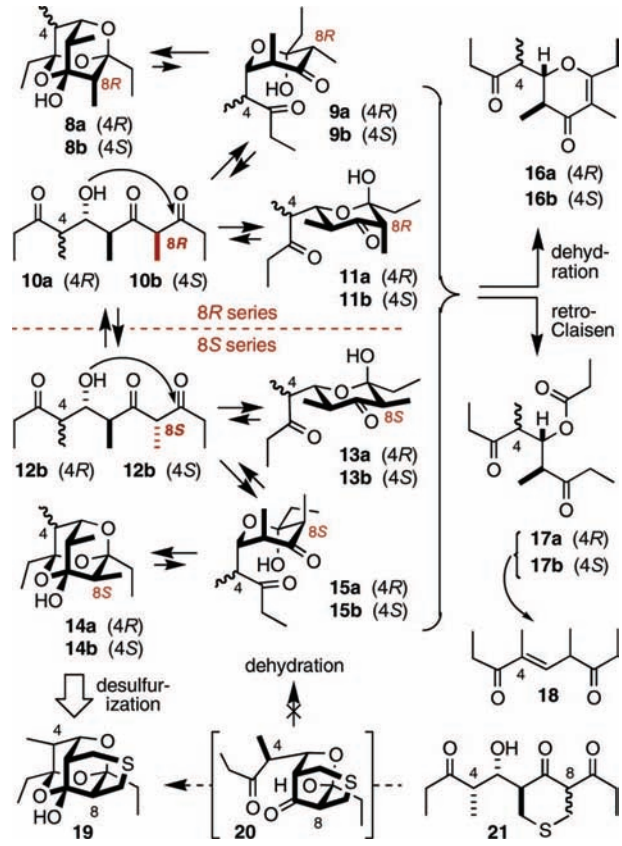


Figure 1. Structural relationships among siphonarin B (**1**), caloundrin B (**2**), baconipyrone C (**3**), and muamvatin (**6**).

The trioxaadamantane ring system is highly unusual and present in only two natural products, the siphonariid polypropionates caloundrin B (**2**)[4] and muamvatin (**6**).[7] The former is known to be unstable,[4] and synthetic studies[8] on the latter suggest that this ring system is sensitive to both acid and base. In contrast to **5**, products from alternate cyclizations of **7** are unknown. The trioxaadamantane ring system is formally derived from ring-chain tautomerism of a 3-hydroxy-1,5,7-trione (Scheme 1). Although this ring system is thermodynamically stable, its formation is impeded because it proceeds via the less stable of the intermediate hemiacetal anomers (i.e., **9** and **15** vs **11** and **13**), and these hemiacetals readily undergo dehydration (to **16**) or retro-Claisen (to **17**) under acidic and basic conditions. Consequently, the precursor hydroxytrione (i.e., **10** or **12**) must be unveiled under very mild conditions. We reasoned that by exploiting a thiopyran template[9] like **21**, formation of sulfur-bridged trioxaadamantane **19** under acidic conditions would be facilitated because the required intermediate hemiacetal anomer **20** is the more stable and its dehydration is disfavored by Bredt's rule[10] (Scheme 1). Desulfurization of **19** would lead to the thermodynamically unstable trioxaadamantane **14b** that should be readily transformed into the desired **8b** or other congeners (e.g., **13b** and **17b**; cf. **1**−**3**) under controlled conditions.

Scheme 1. Trioxaadamantanes from 3-Hydroxy-1,5,7-triones



To test the above hypothesis, we set out to prepare the known trioxaadamantane **8a**[8d] related to muamvatin (**6**). Aldol reaction of the enol borinate of (±)-**24**[11] with propanal gave the adduct (±)-**25** as a 9:1 mixture of diastereomers

(6) Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1994**, *35*, 6929–6932.

(7) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680–6682.

(8) (a) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610. (b) Hoffmann, R. W.; Dahmann, G. *Tetrahedron Lett.* **1993**, *34*, 1115–1118. (c) Dahmann, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1994**, 837–845. (d) Hoffmann, R. W.; Dahmann, G. *Chem. Ber.* **1994**, *127*, 1317–1322. Also see: (e) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827–1830.

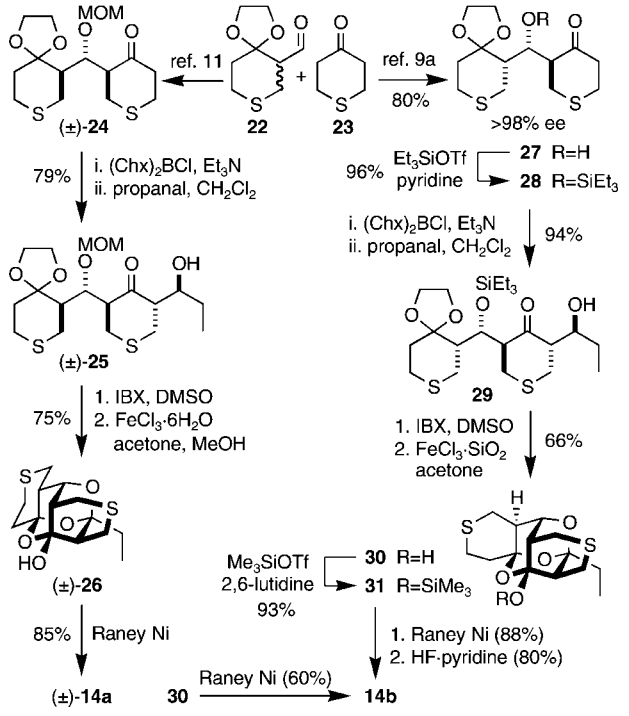
(9) Recent synthetic applications of the thiopyran route to polypropionates: (a) Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989–8992. (b) Jheengut, V.; Ward, D. E. *J. Org. Chem.* **2007**, *72*, 7805–7808.

(10) (a) Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219–274. (b) Buchanan, G. L. *Chem. Soc. Rev.* **1974**, *3*, 41–63.

(11) (a) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618–1629. (b) Ward, D. E.; Sales, M.; Sasmal, P. K. *J. Org. Chem.* **2004**, *69*, 4808–4815.

(Scheme 2).[12] Oxidation of (±)-**25** with IBX followed by treatment with $FeCl_3$·$6H_2O$ in refluxing acetone/MeOH[13] served to remove the acetal protecting groups and catalyze the formation of the unusual trioxadithiapentacycle (±)-**26** in good yield. Finally, desulfurization of (±)-**26** with Raney Ni proceeded smoothly to provide trioxaadamantane (±)-**14a**, whose structure was confirmed by X-ray crystallography.

Scheme 2. Synthesis of Trioxaadamantanes **14a** and **14b**



Trioxaadamantane **14a** is thermodynamically unstable relative to **8a** (Scheme 1); however, **14a** was surprisingly stable kinetically. Our attempts to catalyze the isomerization of **14a** to **8a** are summarized in Table 1. Absorption of **14a** onto silica gel according to Paterson's procedure[8a] produced **8a** very slowly (entries 1 and 2). Reaction of **14a** with HF·pyridine at rt as described by Hoffmann[8b−d] also produced **8a**, albeit exceedingly slowly. The isomerization was accelerated at 40 °C; however, small amounts of **16a**[8d] were detected at longer reaction times (entries 5 and 6). In analogy to Perkins' report,[8e] treatment of **14a** with DBU in C_6D_6 solution gave **8a** in addition to **18** (entries 7−9). The formation of **18** presumably results from elimination of propanoic acid from the initially formed retro-Claisen ester (±)-**17a**. Alternatively, a warm solution of **14a** and imidazole[11b] in $CDCl_3$ cleanly produced **8a** in 85% isolated yield (entry 12).

Table 1. Isomerization of (±)-**14a** to (±)-**8a**.

				product distribution (%)[a]			
entry	conditions	temp	time	**14a**	**8a**	**16a**	**18**
1	silica gel[b]	rt	1 d	85	15		
2		rt	5 d	35	65		
3	HF·py/py/H_2O[c]	rt	1 d	95	5		
4		rt	7 d	70	30		
5		40 °C	1 d	30	70		
6		40 °C	5 d		95	5[d]	
7	DBU/C_6D_6[e]	rt	2 d	6	83		11[d]
8		rt	5 d	1	82		18[d]
9		rt	10 d		30		70[d]
10	imidazole/$CDCl_3$[f]	rt	1 d	>95	<5		
11		40 °C	1 d	30	70		
12		40 °C	4 d		100[g]		

[a] By ^{1}H NMR. [b] Absorption of a CH_2Cl_2 solution of **14a** onto silica gel 60 (a 0.25 mm PTLC plate) followed by elution after the indicated time. [c] Pyridine (1.2 mL), HF·pyridine (0.4 mL), and H_2O (50 μL) were added to a solution of **14a** (10−20 mg) in THF (2 mL). [d] Tentatively identified. [e] DBU (0.02 M; ca. 1 equiv). [f] Imidazole 0.6 M; **14a** < 0.1 M. [g] 85% isolated yield on a 20 mg scale.

We next attempted to prepare the less stable trioxaadamantane **8b** related to caloundrin B (**2**). Readily available enantiopure **27**,[9a] protected as its trimethylsilyl ether **28**, was subjected to boron-mediated aldol reaction with propanal to give the adduct **29**[12] in excellent yield (Scheme 2). In analogy to the synthesis of (±)-**26**, IBX oxidation of **28** followed by treatment with $FeCl_3$-impregnated silica gel[14] provided the trioxadithiapentacycle **30** (X-ray) in moderate yield. Raney Ni desulfurization of **30** gave **14b**; however, the yield was variable and much lower than was obtained from (±)-**26**, perhaps reflecting the lower stability of **14b** compared to **14a** (vide infra). Alternatively, similar desulfurization of **31** cleanly gave the trimethylsilyl ether of **14b** (88%) that was converted to **14b** (80%) by brief treatment with HF·pyridine.[15]

Under the same conditions as applied to **14a**, isomerizations of **14b** were much more facile and gave a greater diversity of products (Table 2). For example, **14a** was relatively stable to silica gel, but similar treatment of **14b** (entry 1) gave a mixture of trioxaadamantane (**8b** and **14b**), hemiacetal (**13b**), dihydropyrone (**16b**), and retro-Claisen ester (**17b**) products. Whereas **14a** was smoothly isomerized to **8a** by HF·pyridine at 40 °C, only the dihydropyrone **16b** was obtained from **14b** under those conditions (entry 5); however, at room temperature the hemiacetal **13b** accumulated and could be isolated in moderate yield (entry 3). Interestingly, exposure of **13b** to HF·pyridine produced a 5:1 mixture of **8b** and **14b** at low conversion demonstrating the reversible formation of **14b** (entries 6 and 7). In contrast to **14a**, treatment of **14b** with DBU in C_6D_6 rapidly gave

(12) The indicated relative configuration of the adduct was not rigorously determined but is based on the precedent established in: Ward, D. E.; Beye, G. E.; Sales, M.; Alarcon, I. Q.; Gillis, H. M.; Jheengut, V. *J. Org. Chem.* **2007**, *72*, 1667–1674.

(13) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686. Addition of MeOH was required to facilitate efficient removal of the MOM group.

(14) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404–406.

(15) The isolated yield of **14b** was diminished by its sensitivity to silica gel (Table 2, entry 1). Attempted deprotections with TBAF/THF (rapid decomposition) and with $HF_{(aq)}$/MeCN (quantitative formation of **16b**) did not give detectable amounts of **8b**, **13b**, **14b**, or **17b**. Only **16b** was obtained when the order of steps was reversed; i.e., desulfurization of **28** followed by IBX oxidation and treatment with $FeCl_3$/acetone.

Table 2. Isomerizations of **14b**, **13b**, **8b**, and **17b**

					product distribution (%)[a]					
entry	SM[b]	conditions	temp	time	**14b**	**8b**	**13b**	**16b**	**17b**	**18**
1	**14b**	silica gel[c]	rt	1 d	13	31	9	24	33	
2	**14b**[d]	HF·py/py/H_2O[e]	rt	2 h	86		9	5		
3			rt	2 d	22	15	56[f]	7		
4			rt	5 d	4	57	30	9		
5			40 °C	4 d				>90		
6	**13b**		rt	1 d	7	36	44	13		
7			rt	3 d	10	44	31	15		
8	**14b**	DBU/C_6D_6[g]	rt	2 h	26	22	12		40	
9			rt	1 d		31			63[h]	6[i]
10	**8b**		rt	1 d		67		4	26	3[i]
11			rt	7 d		40		7	37	15[i]
12			rt	18 d		30		2	36	32[i]
13	**13b**		rt	8 h		33			67	
14	**17b**		rt	1 d					55	45[i]
15			rt	7 d						>90[i]
16	**14b**	imidazole/$CDCl_3$[j]	rt	2 d	19	65	10	2	4	
17			rt	5 d		76[k]	10		14	
18	**8b**		rt	5 d		>90				
19	**13b**		rt	1 d	5	67	16		12	

[a] By ^{1}H NMR. [b] Starting material. [c] Absorption of a CH_2Cl_2 solution of **14b** onto silica gel 60 (0.25 mm PTLC plate) followed by elution after the indicated time. [d] The Me_3Si ether of **14b** was used. [e] Pyridine (1.2 mL), HF·pyridine (0.4 mL), and H_2O (50 μL) were added to a solution of SM (10−20 mg) in THF (2 mL). [f] 49% isolated yield on 40 mg scale. [g] DBU (0.02 M; ca. 1 equiv). [h] 47% isolated yield on a 45 mg scale. [i] Tentatively identified by NMR but not isolated; see the Supporting Information for details. [j] Imidazole 0.6 M; **14b** < 0.1 M. [k] 77% isolated yield on a 16 mg scale.

ca. a 1:2 mixture of **8b** and **17b**, respectively (entries 8 and 9), presumably via the intermediacy of **13b** (entry13). Similar treatment of **8b** also produced **17b** although much more slowly (entries 10−12). In all cases, treatment with DBU led to **18** via elimination of propanoic acid from **17b** (entries 9−15). Imidazole catalyzed the isomerization of **14b** at room temperature to predominantly give **8b** along with smaller amounts of **11b** and **17b** (entries 16 and 17). A similar product mixture was obtained from **13b**, a result that also confirmed the reversible formation of **14b** (entry 19). Thus, any of **8b**, **13b**, **16b**, **17b**, or **18** can be obtained as the major product from **14b** by varying the conditions.

Despite the very close structural relationship between **14a** and **14b**, their isomerization behavior is remarkably different. In an attempt to identify the reasons for these differences, we analyzed the isomerizations computationally (Figure 2).[16] In contrast to the structures in Scheme 1, the preferred conformation of **15b** was found to be the chair with equatorial methyl groups, and those of **9a** and **15a** were twist-boats stabilized by H-bonding. The more facile isomerizations of **14b** compared to **14a** (cf. Tables 1 and 2) and to **8b** (Table 2, entries 9 and 10) are consistent with the differences in energies between those trioxaadamantanes and their hemiacetal precursors (**14b**−**15b**, 16.8 kJ/mol; **14a**−**15a**, 23.8 kJ/mol; **8b**−**9b**, 32 kJ/mol).[17] The lack of intermediates observed in the isomerization of **14a** to **8a** (Table 1) can be rationalized by considering the much smaller differences in energies between **13a** and **9a** (7.3 kJ/mol) vs **15a** (13.3 kJ/mol) (i.e., transformation of **13a** to **8a** should be faster than that of **14a** to **13a**) and the low equilibrium concentration expected for **13a**.[17] Although a similar analysis of **9b**, **13b**, and **15b** supports a greater persistence and equilibrium concentration of **13b** (i.e., facilitating more elimination and retro-Claisen) compared to **13a**, it does not account for the significant accumulation of **13b** on treatment of **14b** with HF·pyridine.

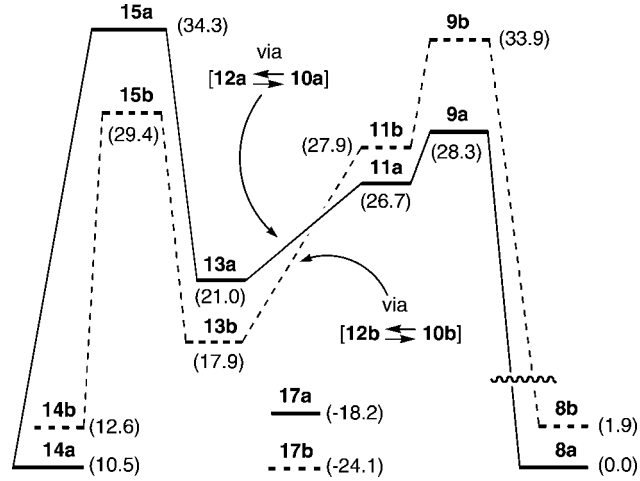


Figure 2. B3LYP/6-31G** energies (kJ/mol) for **8**, **9**, **11**, **13**, **14**, **15**, and **17** relative to **8a**.

In conclusion, isomerization of **14b** under different conditions leads selectively to **13b**, **8b**, or **17b**, synthetic models of key structural motifs present in siphonarin B (**1**), caloundrin B (**2**), and baconipyrone C (**3**), respectively. Application of this approach to an analogous derivative of **5** might clarify the relationships among these polypropionates and allow their synthesis from a common intermediate. We are currently pursuing that objective.

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Supporting Information Available: Experimental and computational procedures, spectroscopic data, X-ray data (CIF), structure determinations, and NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) See the Supporting Information for details.

(17) The computed energies are for ground states; reaction barriers will be higher in energy. Predicitions of relative reaction facilities are based on Hammond's postulate (i.e., more stable intermediates are formed faster).