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Synthesis and Characterization of Cyclopropylpolyketides: A Combined Experimental and Theoretical Study

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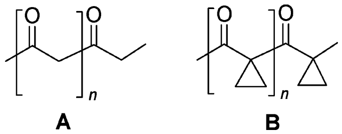
The first open-chain cyclopropylpolyketides were prepared and characterized by experimental and computational methods.

Introduction

A great variety of pharmacologically important natural products are biosynthetically derived from poly(β-oxo)-carboxylic acids (polyketides).[1] Polyketides and related 1,3-oligocarbonyl derivatives also represent important synthetic building blocks (e.g. for the synthesis of polyols by stereoselective reduction).[2] Harris and co-workers reported the biomimetic synthesis of various polyketides **A** based on the condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with carboxylic acid derivatives (Figure 1).[3] Tetraketides and their higher homologues are unstable and rapidly undergo an intramolecular aldol condensation to give polyhydroxylated arenes. Therefore, open-chain polyketides are unknown to date. An exception are 3,5-dioxopimelates which contain two terminal ester groups and thus cannot undergo an intramolecular aldol condensation.[4] The same is true for hitherto unknown oligocyclopropanes **B** which are, in a formal sense, analogues of polyketides lacking the CH-acidic methylene groups.[5,6] Cyclopropyl-based molecular architectures are of considerable theoretical and structural interest.[7] In recent years, versatile synthetic approaches to open-chain oligocyclopropanes[8] and σ-[*n*]helicenes[9] have been developed. Trispiro-[2.1.2.1.2.1]dodecane-4,8,12-trione, which can be regarded as a *cyclic* cyclopropyltriketide, was prepared in low yield by a Zn/Cu-mediated transformation of 1-bromocyclopropanecarboxylic chloride.[10]



A **B**

Figure 1. General structures of open-chain polyketides.

Results and Discussion

Our strategy for the synthesis of cyclopropylpolyketides relies on a straightforward sequence of chain elongation by acylation and subsequent cyclopropanation (Scheme 1, Table 1). The K_2CO_3-mediated[11] cyclopropanation of 1-(cyclopropyl)butane-1,3-dione and benzoylacetone with 1,2-dibromoethane afforded the cyclopropanes **2a** and **2b**.[12] The LDA-mediated reaction of **2a** with cyclopropanecarboxylic chloride gave **3a** in up to 65% yield. Likewise, the condensation of **2b** with cyclopropanecarboxylic chloride and benzoyl chloride afforded **3b** and **3c**, respectively. Products **3a–c** exist as mixtures of keto-enol tautomers. The cyclopropanation of **3a–c** with 1,2-dibromoethane afforded the desired cyclopropyltriketides **4a–c**. During the optimization, the stoichiometry and the concentration played an important role. The structure of **4c** was independently confirmed by an X-ray crystal structure analysis (Figure 2).[13]

The reaction of dimethyl cyclopropane-1,1-dicarboxylate (**5**) with 1-cyclopropylethan-1-one afforded **7** which was transformed into triketide **8** (Scheme 2). The best yield of **7** was obtained when sodium methoxide and MTBE were used as base and solvent, respectively. Noteworthy, the use of KO*t*Bu or LDA was unsuccessful, as it led to a retro-Claisen reaction.

The NaOMe-mediated reaction of **5** with **2a** afforded the cyclopropyltetraketide **9** which represents a rare example of

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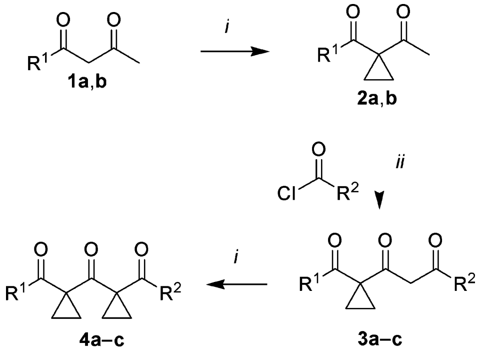


Scheme 1. Synthesis of cyclopropyltriketides **4a**–**c**. Conditions: *i*: 1,2-dibromoethane (2.0 equiv.), K_2CO_3 (4.0 equiv.), DMSO, 20 °C, 8 h; *ii*: (1) LDA (1.2 equiv.), THF, –78 °C, 1 h, (2) acyl chloride, –78 → 20 °C, 12 h.

Table 1. Synthesis of cyclopropyltriketides **4a**–**c**.

2	3,4	R^1	R^2	% of **2**[a]	% of **3**[a]	% of **4**[a]
a	**a**	cPr	cPr	70	65	30
b	**b**	Ph	cPr	75	47	64
b	**c**	Ph	Ph	75	22	30

[a] Isolated yields.

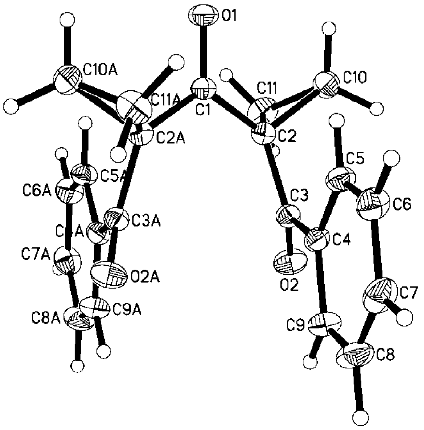
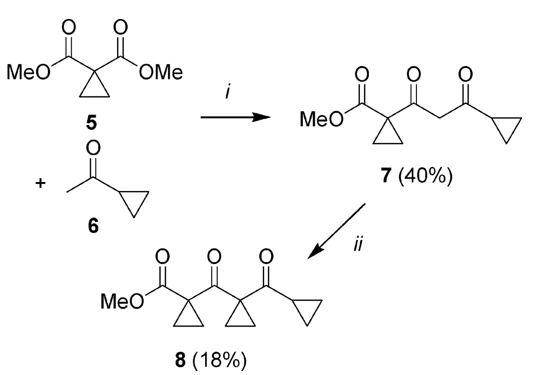
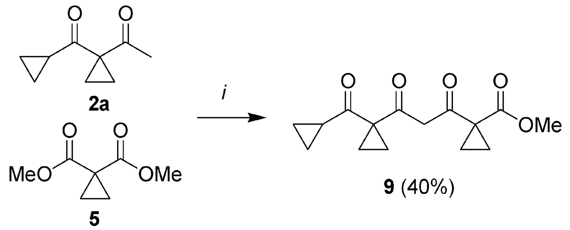


Figure 2. ORTEP plot of **4c**.



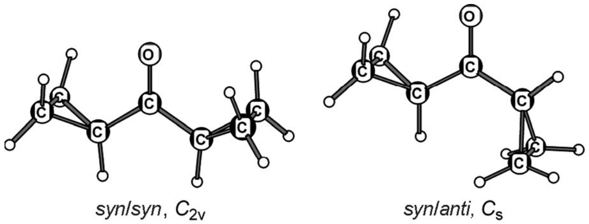
Scheme 2. Synthesis of cyclopropyltriketide **8**. Conditions: *i*: (1) NaOMe, MTBE, 30 °C, 3 h, (2) HCl (10%); *ii*: 1,2-dibromoethane (2.0 equiv.), K_2CO_3 (4.0 equiv.), DMSO, 20 °C, 8 h.

an open-chain tetraketide (Scheme 3). The cyclopropanation of **9** proved to be unsuccessful under various conditions.



Scheme 3. Synthesis of cyclopropyltetraketide **9**. Conditions: *i*: (1) NaOMe, MTBE, 30 °C, 3 h, (2) HCl (10%).

We have also carried out B3LYP6-311+G(d,p)[14] density functional theory computations on the structural and energetic properties of the cyclopropylpolyketides using the Gaussian 03 program package.[15] The B3LYP/6-311+G(d,p) method has been benchmarked on the basis of the comparison between the computed and experimentally determined relative energy and structural parameters of dicyclopropyl ketone (Figure 3).



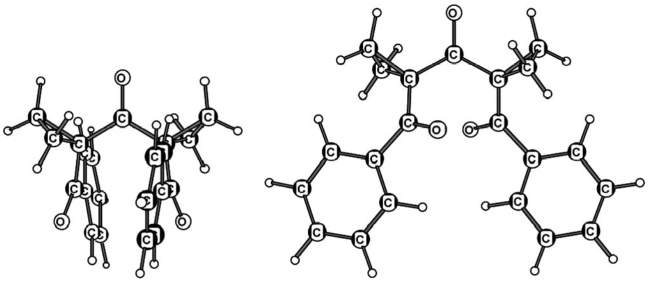
syn/*syn*, C_{2v}
(0.00 kcal/mol, 92.3%)

syn/*anti*, C_s
(1.78 kcal/mol, 7.7%)

Figure 3. Conformation and energy of dicyclopropyl ketone.

It has been shown experimentally that dicyclopropyl ketone possesses one *syn*/*syn* and one *syn*/*anti* conformation.[16] The *syn*/*syn* conformer (93%) has two cyclopropyl rings pointing towards the oxygen atom of the carbonyl group; the *syn*/*anti* conformer (7%) has one cyclopropyl ring pointing towards and one pointing away from the carbonyl group. Along with the perfect agreement of the bonding parameters (see Supporting Information), the computed relative free energy of 1.78 kcal/mol gives a ratio of 92.3%:7.7% which is also in perfect agreement with the experiment.

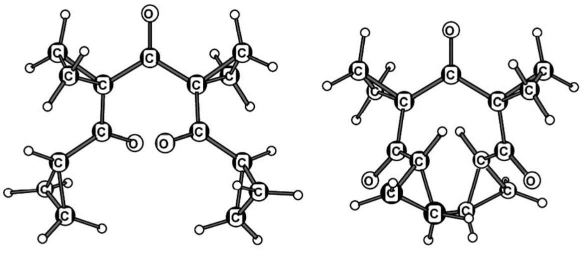
The computed most stable conformer of **4c** (Figure 4) is in perfect agreement with the X-ray crystal structure analysis (Figure 2). The two cyclopropyl rings have a *syn* conformation to the central carbonyl group, and the carbonyl groups of the benzoyl groups also exist in a *syn* conformation to the cyclopropyl rings (*syn*/*syn*; *syn*/*syn*). A closer inspection shows that the C1–O1 and C2–C10 bonds exist in an eclipsed orientation with a torsional angle of 9.55° (calcd. 0.04°), and the C2–C11 and C3–O2 bonds are also in an eclipsed orientation with a torsional angle of –15.11° (calcd. –18.05°). Apart from the *syn*/*syn*; *syn*/*syn* conformer, we have found another conformer having a *syn*/*syn* conformation of the two cyclopropyl groups to the central ketone group, but an *anti*/*anti* conformation of the two benzoyl substituents. However, the latter conformer is 9.32 kcal/mol higher in energy than the former one, and thermodynamically not competitive (Figure 4). Detailed inspection of the IR spectrum of **4c** (ATR) shows two sharp C=O bands (assigned to the central and to the benzoyl carbonyl groups) which have been confirmed by the computations. This result shows that only one conformer is present.


syn/*syn*; *syn*/*syn*, C_2 (0.00 kcal/mol)

syn/*syn*; *anti*/*anti*, C_2 (9.32 kcal/mol)

Figure 4. Conformation and energy of **4c**.

For triketide **4a** also two conformers were found which have structures like those of derivative **4c**. In one conformer all cyclopropyl rings are oriented *syn* to the carbonyl groups, while the other one has a cyclopropylcarbonyl group *anti* to the cyclopropyl groups. However, both conformers are very close in free energy (0.06 kcal/mol) which results in an equilibrium ratio of 52%:48% (Figure 5). The IR spectrum of **4a** (neat) shows a broad C=O band which suggests that more than one conformer is present. ^{1}H and ^{13}C NMR experiments at about –100 °C may also be taken as evidence of such an interconversion with a low activation barrier (line broadening observed predominantly for the CH_2 signals of the central cyclopropane). However, as neither coalescence nor the region of slow exchange were reached, the nature of interconverting species remains speculative.


syn/*anti*/*syn*; *syn*/*anti*/*syn*, C_2 (0.00 kcal/mol)

syn/*syn*/*syn*; *syn*/*syn*/*syn*, C_2 (0.06 kcal/mol)

Figure 5. Conformation and energy of **4a**.

Conclusions

The first open-chain cyclopropylpolyketides were prepared and characterized by experimental and computational methods. We currently study the chemical behavior of cyclopropylpolyketides and the synthesis of higher homologues.

Experimental Section

General Procedure for the Synthesis of Cyclopropyloligoketides 4: To a suspension of K_2CO_3 (4.0 equiv.) in DMSO (0.3–0.5 mL/mmol) was added **3** (1.0 equiv.). To the reaction mixture was added dropwise dibromoethane (2.0 equiv.) at 20 °C with vigorous stirring. After stirring at 20 °C for 8 h, K_2CO_3 was removed by filtration. The solid was thoroughly washed with diethyl ether. The filtrate was washed with water until the yellow colour had disappeared, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to give product **4**.

Synthesis and Spectroscopic Data of 4a: Starting with **3a** (0.500 g, 2.27 mmol), dissolved in a suspension of K_2CO_3 (0.784 g, 5.68 mmol) in DMSO (0.7 mL) and 1,2-dibromoethane (0.2 mL, 2.27 mmol), **4a** was isolated as a colorless oil (0.17 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 and 1.02 (2 m, 2 H each, CH_2), 1.63 (AA′BB′, 4 H, CH_2), 1.86 (tt, 2 H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (CH_2), 17.6 (CH), 19.3 (CH_2), 43.2 (C), 202.1, 205.5 (CO) ppm. IR (neat): $\tilde{\nu}$ = 3096 (m), 3011 (s), 1681 (s, br.), 1570 (m), 1444 (s), 1392 (s, br.), 1319 (s), 1280 (s), 1198 (m), 1107 (s), 1085 (s), 1061 (s), 1006 (s), 953 (m), 936 (w), 922 (w), 893 (m), 841 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 246 (0.3) [M$^+$], 218 (82.9), 203 (17.7), 177 (19.4), 121 (15.0), 69 (100). $C_{15}H_{18}O_3$ (246.30): calcd. C 73.15, H 7.37; found C 73.30, H 7.36.

Supporting Information (see footnote on the first page of this article): Experimental procedures, compound characterization, copies of VT-NMR spectra, and details of the computations.

Acknowledgments

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[1] a) J. Staunton, K. J. Weissman, *Nat. Prod. Rep.* **2001**, *18*, 380; b) A. M. P. Koskinen, K. Karisalmi, *Chem. Soc. Rev.* **2005**, *34*, 677.

[2] For ethyl 3,5-dioxohexanoate, see for example: a) A. G. M. Barrett, R. A. E. Carr, M. A. W. Finch, J.-C. Florent, G. Richardson, N. D. A. Walshe, *J. Org. Chem.* **1986**, *51*, 4254; b) A. G. M. Barrett, T. M. Morris, D. H. R. Barton, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2272.

[3] For a review, see: a) T. M. Harris, C. M. Harris, *Tetrahedron* **1977**, *33*, 2159; see also: b) S. G. Gilbreath, C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1988**, *110*, 6172.

[4] S. Reim, V. T. H. Nguyen, U. Albrecht, P. Langer, *Tetrahedron Lett.* **2005**, *46*, 8423.

[5] Peralkylpolyketides were previously prepared in very low yields based on the base-mediated ring cleavage of 2,2,4-trimethyl-3-hydroxypentenoic acid β-lactone: K. D. Berlin, R. B. Hanson, *J. Org. Chem.* **1967**, *32*, 1763.

[6] The formation of a triketide as a side-product was previously claimed, but the product has not been unambiguously identified: J. M. Stewart, G. K. Pagenkopf, *J. Org. Chem.* **1969**, *34*, 7.

[7] A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926.

[8] M. von Seebach, S. I. Kozhushkov, D. Frank, R. Boese, J. Benet-Buchholz, D. S. Yufit, H. Schill, A. de Meijere, *Chem. Eur. J.* **2007**, *13*, 167.

[9] a) A. de Meijere, A. F. Khlebnikov, S. I. Kozhushkov, K. Miyazawa, D. Frank, P. R. Schreiner, C. Rinderspacher, D. S. Yufit, J. A. K. Howard, *Angew. Chem.* **2004**, *116*, 6715; *Angew. Chem. Int. Ed.* **2004**, *43*, 6553; b) A. de Meijere, A. F. Khlebnikov, S. I. Kozhushkov, D. S. Yufit, O. V. Chetina, J. A. K. Howard, T.

Kurahashi, K. Miyazawa, D. Frank, P. R. Schreiner, B. C. Rinderspacher, M. Fujisawa, C. Yamamoto, Y. Okamoto, *Chem. Eur. J.* **2006**, *12*, 5697.

[10] a) J.-M. Wulff, H. M. R. Hoffmann, *Angew. Chem.* **1985**, *97*, 597; b) H. M. R. Hoffmann, U. Eggert, A. Walenta, E. Weineck, D. Schomburg, R. Wartchow, F. H. Allen, *J. Org. Chem.* **1989**, *54*, 6096; c) A. Wulferding, J. H. Jankowski, H. M. R. Hoffmann, *Chem. Ber.* **1994**, *127*, 1275.

[11] N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, L. S. Surmina, Z. A. Rashchupkina, *J. Org. Chem. USSR (Engl. Transl.)* **1983**, *19*, 474; *Zh. Org. Khim.* **1983**, *19*, 541.

[12] The synthesis of **2a** and **2b** is known; however, compound **2a** was not completely characterized.N. S. Zefirov, S. I. Kozhushkov, T. S. Kuznetsova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1983**, *19*, 644; *Khim. Geterotsikl. Soedin.* **1983**, *19*, 801.

[13] CCDC-660021 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) P. J. Stevens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.

[15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision C.02, Gaussian, Inc., Wallingford CT, **2004**.

[16] M. Traetteberg, P. Bakken, J. V. Quesada, V. S. Mastryukov, J. E. Boggs, *J. Mol. Struct.* **1999**, *485–486*, 73.

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