A facile route to 3,7-*cis*-disubstituted cycloocta-1,5-diene-1,2,5,6-tetracarboxylates through photochemical [2 + 2]cycloaddition of 3-substituted cyclobutene-1,2-dicarboxylates and thermal isomerization†

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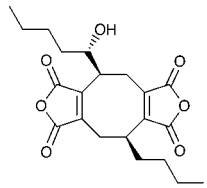
Photochemical dimerization of 3-substituted cyclobutene-1,2-dicarboxylates followed by thermal isomerization gives regio- and stereo-selectively 3,7-*cis*-disubstituted cycloocta-1,5-diene-1,2,5,6-tetracarboxylates.

Cyclooctanoids have been attracting great interest in the fields of agricultural and pharmaceutical chemistry because of their unique structures and biological activities. For example, natural product Zopfiellin[1] was isolated very recently. Synthetic

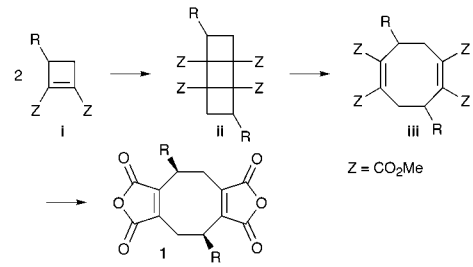


Zopfiellin

methods for cyclooctanoids have been studied over the last few decades.[2] We also reported a route to cyclooctanoids *via* bromination of tetramethyl cycloocta-1,5-diene-1,2,5,6-tetracarboxylate followed by alkylation with organocopper reagents to give rise to regio- and stereo-selectively 3,7-*cis*-disubstitution of the tetraester.[3] This method, however, was restricted to primary alkyl groups due mainly to the low reactivity of secondary and tertiary alkylcopper reagents.

Accordingly, we considered that introduction of bulky groups such as secondary, tertiary and substituted alkyls before eight-membered ring formation would be favorable. In addition, [2 + 2]cycloaddition of cyclobutene looked attractive for eight membered ring formation. Although the synthetic scheme has precedents,[4] we felt it necessary to study carefully the stereochemical and regiochemical outcome of cyclooctanoid synthesis.

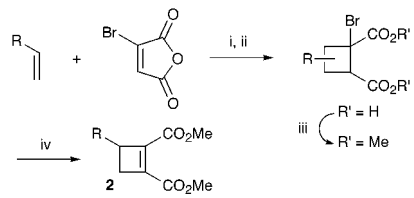
Herein we demonstrate that [2 + 2]cycloaddition is widely applicable to the synthesis of eight-membered ring compounds, especially highly substituted ones, as shown in Scheme 1. Although the dimerization ring opening route is limited to symmetrical cyclooctadiene systems, we considered it important to first establish a reliable synthetic route to cyclooctanoids containing various functional groups. We envisaged that dimeric [2 + 2]cycloaddition of cyclobutene **i** would afford a mixture of tricyclo[4.2.0.0]octanes **ii** which might thermally isomerize to 3,7-*cis*-disubstituted cycloocta-1,5-diene derivative **iii**, a precursor of bisanhydride **1** closely related to Zopfiellin. After many experiments, we were pleased to find that this new synthetic route worked. Many 3,7-*cis*-disubstituted cycloocta-1,5-diene derivatives, including those substituted by secondary and tertiary alkyl groups, could be synthesized regio- and stereo-selectively by this method.



Scheme 1

Key starting materials **2** were prepared from readily available terminal olefins according to the route shown in Scheme 2.[5] Yields of **2** based on the respective olefins are summarized in Table 1. In addition to **2** with a primary alkyl group, those with a secondary or tertiary alkyl group were prepared in good to high yields. Vinyl, bromo and acetoxy groups did not interfere with the reaction (**2g**–**k**). Trimethylsilylmethyl-substituted cyclobutene **2l** was accessible, albeit in a lower yield.

Photochemical dimerization of 3-substituted cyclobutene-1,2-dicarboxylates **2** proceeded smoothly to afford isomeric mixtures of tricyclo[4.2.0.0]octanes, which upon thermal iso-



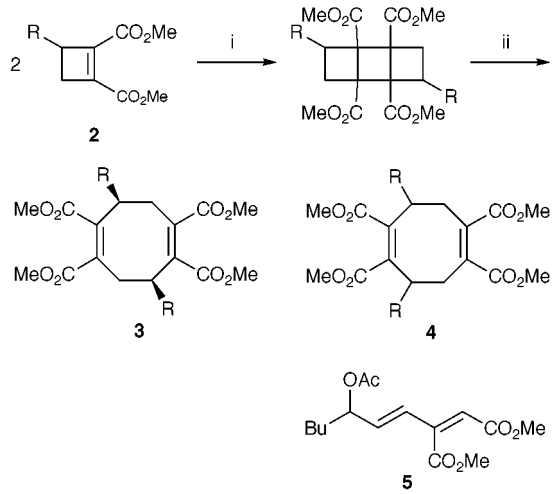
Scheme 2 *Reagents and conditions*: i, *hν*, Ph_2CO, MeCN; ii, aq. Na_2CO_3, then aq. HCl; iii, H_2SO_4, MeOH; iv, DBU, $CHCl_3$.

Table 1 Synthesis of 3-substituted cyclobutene-1,2-dicarboxylates **2**

R	Products	Yield (%)[a]	R	Products	Yield (%)[a]
Pr	**2a**	57	$CH{=}CH_2$	**2g**	24
C_6H_{13}	**2b**	43	CH_2CH_2Br	**2h**	39
Pr^i	**2c**	50	CH_2OAc	**2i**	35
Bu^s	**2d**	23[b]	CH_2CH_2OAc	**2j**	38
CHMePr	**2e**	51[b]	CH(OAc)Bu	**2k**	16[b]
Bu^t	**2f**	25	CH_2SiMe_3	**2l**	15

[a] Isolated overall yields. [b] Diastereomeric mixture (1 : 1).

† Dedicated to Professor Michinori Ōki on the occasion of his 70th birthday.



Scheme 3 *Reagents and conditions*: i, *hν*, Ph_2CO, MeCN; ii, xylene, reflux; iii, aq. NaOH,MeOH, then aq. HCl.

Table 2 Transformation of **2** to **3**

R	Products	Yield (%)[a]	R	Products	Yield (%)[a]
Pr	**3a**	48	CH=CH_2	**3g**	—[c]
C_6H_{13}	**3b**	49	CH_2CH_2Br	**3h**	38
Pr^i	**3c**	34	CH_2OAc	**3i**	31
Bu^s	**3d**	37[b]	CH_2CH_2OAc	**3j**	20
CHMePr	**3e**	22[b]	CH(OAc)Bu	**3k**	—[d]
Bu^t	**3f**	5	CH_2SiMe_3	**3l**	34

[a] Isolated overall yields are given. [b] Inseparable isomeric mixture. [c] Unidentified compounds were obtained. [d] Compound **5** was obtained.

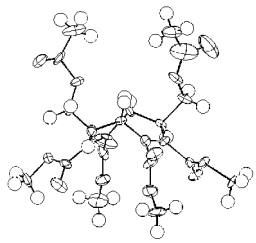


Fig. 1 X-Ray crystallography of **3i**.

merization gave 3,7-*cis*-disubstituted cycloocta-1,5-diene-1,2,5,6-tetracarboxylates **3** as described in Scheme 3.

The results with **2a-l** are listed in Table 2. The possible regioisomer, 3,8-disubstituted cyclooctadiene **4**, was not isolated in all cases. In addition to **2a**, secondary alkyl substituted cyclobutenes **2c**, **2d** and **2e** were smoothly converted into **3c**, **3d** and **3e**, respectively.[6] *tert*-Butyl-substituted cyclooctadiene **3f** was also obtained but in 5% yield. Although **2g** (R = vinyl) gave unidentified compounds, **2h** (R = CH_2CH_2Br), **2i** (R = CH_2OAc) and **2j** (R = CH_2CH_2OAc) were transformed to cyclooctadienes **3h**, **3i** and **3j**, respectively, in moderate yields. These are potential precursors for further elaboration of side chains. The stereochemistry of **3i**[7] was proved to be 3,7-*cis* by X-ray crystallography (Fig. 1). Unexpected product **5** (13%) *in lieu* of **3k** was formed from cyclobutene **2k**. Similarly **2l** was converted into **3l**.

Regio- and stereo-selective formation of **3** is worthy of note. We consider that the dimerization of 3-substituted cyclobutene-1,2-dicarboxylates **2** would take place through diagonal aggregates due to steric repulsion to afford a single regioisomer of the bicyclo[4.2.0.0]octane tetracarboxylates which, upon heating, give thermodynamically favorable 3,7-*cis*-disubstituted cyclooctadienes **3**.

Dipropyl- and diisopropyl-substituted cyclooctadiene tetraesters **3a** and **3c** were converted into the corresponding bisanhydrides **1a**[8,9] (Fig. 2) and **1c** by alkaline hydrolysis and

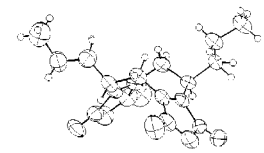
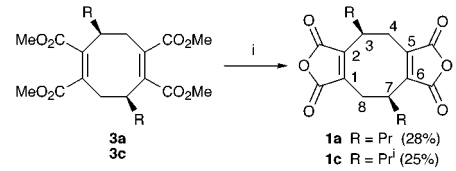


Fig. 2 X-Ray crystallography of **1a**.



Scheme 4 *Reagents and conditions*: i, aq. NaOH,MeOH, then aq. HCl.

subsequent acidification (Scheme 4). Fungicidal activities of **1a** and **1c** were shown to be close to that of Zopfiellin.[9]

In summary, we have disclosed that facile photochemical [2 + 2]cycloaddition of 3-substituted cyclobutene-1,2-dicarboxylates followed by thermal isomerization affords regio- and stereo-selectively 3,7-*cis*-disubstituted cycloocta-1,5-diene-1,2,5,6-tetracarboxylates in moderate to good yields. Further mechanistic study of the regio- and stereo-selectivity of this new synthetic strategy is in progress.

We are grateful to the Analytical Chemistry Division of Nissan Chemical Industries Ltd. for analytical support.

Notes and references

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6 Products **3d** and **3e** formed as inseparable mixtures of isomers due to asymmetric carbons of side chains.

7 *Crystal data* for $C_{22}H_{28}O_{12}$ **3i**: M = 484.00, monoclinic, $C2/c$, a = 16.866(3), b = 10.100(2), c = 14.408(3) Å, β = 93.43(2)°, U = 2450.0(8) Å^3, T = 298 K, Z = 4, μ(Cu-Kα) = 1.009 mm^{-1}, 1980 reflections measured, 1873 unique (R_{int} = 0.065), R = 0.114, R_w = 0.117. *Selected data* for **3i**: $\delta_H(CDCl_3)$ 2.07 (s, 6H), 2.62 (dd, J_1 = 14.2, J_2 6.3, 1H), 3.15 (t, J 14.0, 1H), 3.28–3.38 (m, 1H), 3.74 (s, 6H), 3.76 (s, 3H), 4.24 (dd, J_1 11.2, J_2 4.9, 1H), 4.31 (dd, J_1 11.2, J_2 6.1, 1H); *m/z* (FAB) 485 (M^{+}+1), 453, 425, 411.

8 The stereochemistry of **1a** was confirmed to be 3,7-*cis* by X-ray crystallography, and further suggested the stereoselectivity of this route. *Crystal data* for $C_{18}H_{20}O_6$ **1a**: M = 332.00, monoclinic, $P2_1/a$, a = 11.987(3), b = 13.131(3), c = 11.801(2) Å, β = 112.97(2)°, U = 1710.2(7) Å^3, T = 298 K, Z = 4, μ(Cu-Kα) = 0.7686 mm^{-1}, 2542 reflections measured, 1486 unique (R_{int} = 0.160), R = 0.098, R_w = 0.119. CCDC 182/1355. See http://www.rsc.org/suppdata/cc/1999/1753/ for crystallographic data in .cif format. *Selected data* for **1a**: $\delta_H(CDCl_3)$ 0.98 (t, J 7.2, 6H), 1.41–1.50 (m, 4H), 1.58–1.67 (m, 2H), 1.74–1.83 (m, 2H), 2.91–3.05 (m, 6H).

9 M. Adachi, Y. Nakajima, H. Watanabe, H. Hotta, K. Arai, M. Tagawa, M. Futagawa, T. Furusato, H. Ohya, Y. Baba, C. Noutary, S. Ichikawa, T. Kusumoto and T. Hiyama, 'The 21st IUPAC International Symposium on The Chemistry of Natural Products,' Chinese Chem. Soc., Beijing, 1998, p. 169. Zopfiellin and its analogs **1a** and **1c** exhibit fungicidal activity at 100 ppm (*in vitro*) against *Botorytis cinerea*. Detailed results of the assay will be reported elsewhere.

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