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DIASTEREOSELECTIVE IODOCARBOCYCLIZATION OF 4-PENTENYLMALONATE DERIVATIVES: APPLICATION TO CYCLOSARKOMYCIN SYNTHESIS

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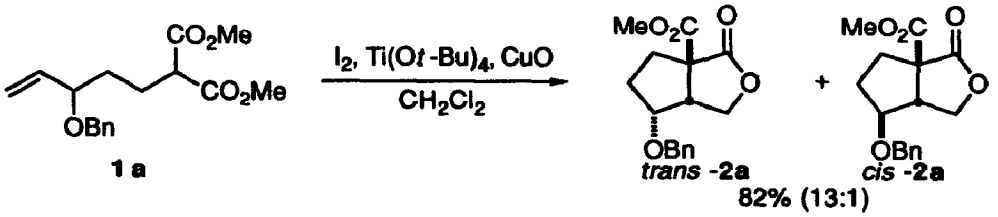
Abstract: *The iodocarbocyclization of 4-pentenylmalonate 1 having a substituent at the 2 or 3 position effectively proceeded by treating 1 with I_2 and $Ti(OtBu)_4$ in the presence of CuO. Stereoelectronic effect of the subtituent at altylic position on diastereoselectivity was notable. As an application of the present reaction, the efficient synthesis of cyclosarkomycin 7 was achieved.*

The halocyclization of unsaturated carboxylic acids, alcohols and amines, mediated by electrophilic reagent, is a useful method for regio- and stereoselective functionalization of double bonds.[1,2] A variety of examples of halocyclization controlled by a substituent in acyclic unsaturated precursors has been reported and applied to the synthesis of organic complex molecules including natural products.[1] On the other hand, so called "halocarbocyclization reaction", in which the carbon nucleophile attacks a double bond activated by an electrophilic halogenating reagent, has not been common.[3] Recently we reported ionic iodocarbocyclization reaction which proceeded by treating 4-pentenylmalonate derivertives with I_2 and $Ti(OR)_4$ to give cyclopentane derivatives in regio- and stereocontrolled manner.[4] In this paper, we report the results of diastereoselectivity (1,2- or 1,3-asymmetric induction) in iodocarbocyclization reaction with 4-pentenylmalonate derivatives having a substituent at the 2 or 3 position. Furthermore, as an application of the present reaction, the efficient synthesis of cyclosarkomycin 7, a precursor of antitumor agent sarkomycin 8[5] from 4-penten-1,3-diol is also described.



At first, the iodocarbocyclization reaction of 3-benzyloxy-4-pentenylmalonate derivative (**1a**) was conducted to investigate the reactivity and diastereoselectivity (Table1). Under the conditions [$Ti(Ot\text{-}Bu)_4$ (1.0 eq), I_2 (1.2 eq), CH_2Cl_2, rt] reported previously,[4] the presence of the substituent at the 3-position resulted in lowering the yield of the desired cyclized product **2a** (28%) along with recovery of starting material **1a** (60%) (entry 1).[6] By increasing the molar ratio of I_2 to 4 equivalents, **2a** was obtained in 82% yield, favoring *trans* - selectivity (*trans:cis* =12:1, entry 3). For this iodocarbocyclization, CuO or Bu_2SnO was found effecitve as an additive. As shown in entry 4, in the presence of CuO and 1.2 eqivalents of I_2, **2a** was obtained in a yield (82%)

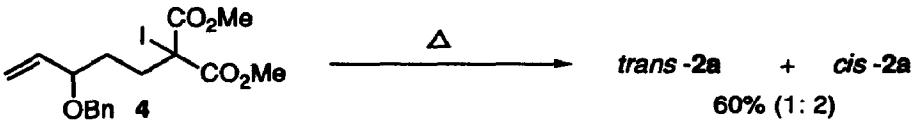
Table 1 Iodocarbocyclization of **1a**[a]

Entry	I_2 (eq)	Additive	Time (h)	**2a** Yield (%)	*trans* : *cis* [b]
1	1.2	–	51	28	10:1
2	2.0	–	12	58	7:1
3	4.0	–	10	82	12:1
4	1.2	CuO [c]	40	82	13:1
5	1.2	Bu_2SnO [c]	40	63	17:1
6	1.2	Bu_4NI [c]	24	0 [d]	–

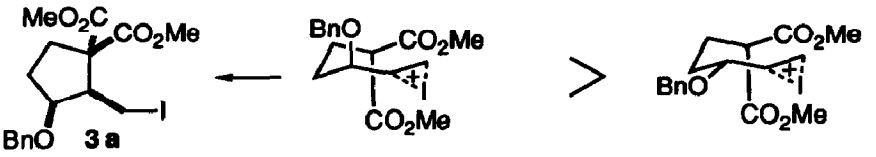
[a] Iodocarbocyclization : **1a** (0.5 mmol), I_2 (see Table 1), $Ti(Ot\text{-}Bu)_4$ (0.5 mmol), CH_2Cl_2 (5 ml), rt.
[b] Determined by ^{1}H-NMR (400MHz). [c] 1.2 eq. [d] No reaction.

comparable to that on using 4 equivalents of I_2, and similar high *trans*-selectivity of **2a** (*trans* : *cis* =13:1) was observed. However, the addition of tetrabutylammonium iodide, possibly a source of I^- in the reaction medium, completely prevented the reaction (entry 6). The main role of CuO and Bu_2SnO would thus appear to accelerate the transformation of intermediate iodide **3a** into lactone **2a** through internal nucleophilic displacement.

As mentioned above, the iodocarbocyclization with **1a** having a BnO substituent at the 3 position afforded *trans*-**2a** as the major product. This is a sharp contrast to the radical iodo atom-transfer reaction of the corresponding iodomalonate **4**[3b] (80°C, 2h) to give **2a** with low *cis*-selectivity.

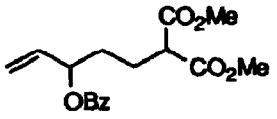
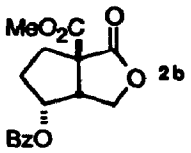
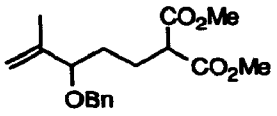
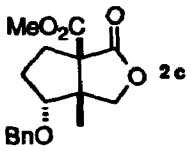
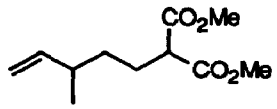
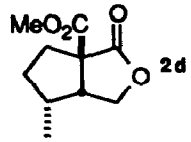
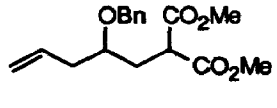
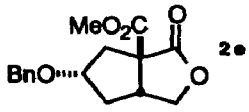
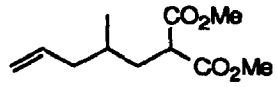
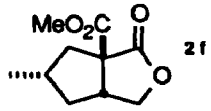
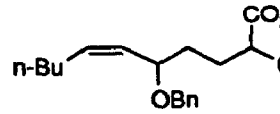
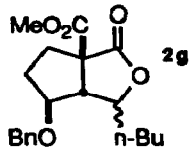


It should be pointed out that the high diastereoselectivity in iodocarbocyclization of **1a** leading to *trans*-**2a** is similar to that in the iodolactonization of 3-benzyloxy-4-pentenoic acid under kinetic control.[1b,7] The observed selectivity may possibly be due to the preferrable axial orientation of the oxygenated substituent (BnO) in the chair like transition state to minimize the overlap of the π-orbital on the double bond at the site of the iodonium ion and σ*orbital on the C-O bond.[7,8]



Further investigation on diastereoselectivity in the iodocarbocyclization was conducted with substrates differing in nature and position of substituents (Table 2). As indicated in Table 2, iodocarbocyclization proceeded in good yield by adding CuO to the I_2, $Ti(Ot\text{-}Bu)_4$ system. With substrate **1b** having a BzO substituent in place of the BnO substituent, slightly lower *trans*-selectivity (**2b**, *trans* :*cis* =8:1) was observed (entry 1), possibly due to decreased electron density of the double bond.[7,8] With substrate **1c** having a methyl substituent at the 4 position, bicyclic lactone **2c** was obtained with excellent diastereoselectivity (entry 2). As shown in the cases of **1a**-**1c**, the stereoelectronic effect of the oxygenated substituent at the allylic position on diastereoselectivity was remarkable as compared with that of alkyl substituent. That is, with **1d** having a methyl group, very low diastereoselectivity of the cyclized product (**2d**, *trans* :*cis* =2:1) was realized (entry 3).[9] In the

Table 2 Iodocarbocyclization of Substituted 4-pentenylmalonates[a]

Entry	Substrate 1	Time (h)	Product[b]	Yield (%)[c]	*trans* :*cis* [d]
1	 1b	30	 2b	92[e]	8:1
2	 1c	6	 2c	73	53:1
3	 1d	18	 2d	79	2:1
4	 1e	24	 2e	83	6.5:1
5	 1f	38	 2f	88	6.3:1
6	 1g	38	 2g	29	–[f]

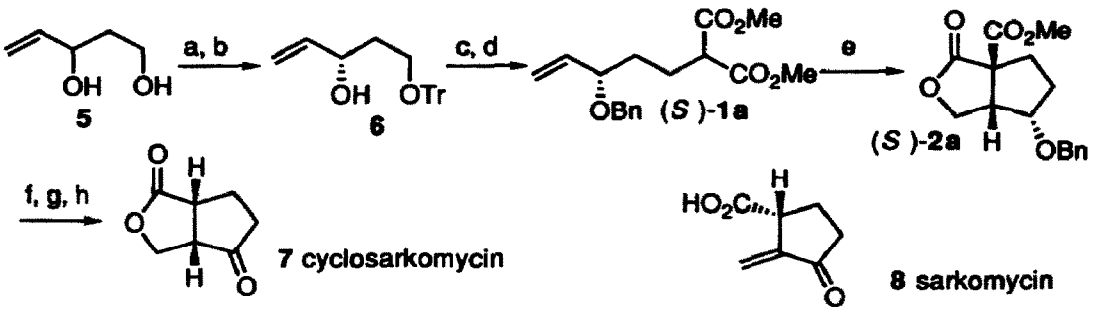
[a] Reaction conditions: 1 (0.5 mmol), $Ti(Ot\text{-}Bu)_4$ (1 eq), I_2 (1.2 eq), CuO (1.2 eq), CH_2Cl_2 (5 ml), rt.

[b] Structure of major isomer is shown. [c] Isolated yield. [d] Determined by ^{1}H-NMR (400MHz).

[e] To complete lactonization, the reaction mixture of the iodocarbocyclization was briefly heated at 140°C. [f] Relative stereochemistry of the BnO group and angular hydrogen was only *cis* ; *trans* : *cis* ratio was 6:1 based on the stereogenic center having *n*-Bu group.

case of substrate having a BnO or methyl substituent at the homoallylic position (2-position of 4-pentenylmalonate), moderate 1,3-asymmetric induction was observed to give bicyclic lactone **2e** (*t*/*c*=6.5) and **2f** (*t*/*c*=6.3), respectively (entries 4, 5). The direction of asymmetric induction was similar to that of iodolactonization of 4-pentenoic acid derivatives having the same substituent mode under kinetic control,[7,9] but opposite to that of iodoetherification.[10] Addition of an alkyl substituent at the terminal position of olefinic moiety caused severe retardation of the iodocarbocyclization reaction and different diastereoselectivity of the product. Thus, *Z*-isomer **1g** gave the cyclized product **2g** in 29% yield with *cis*-selectivity based on the relative stereochemisty between the BnO group and angular hydrogen (entry 6).[7]

Finally, as an application of the present diastereoselective iodocarbocyclization, we achieved the high yield synthesis of cyclosarkomycin **7**, which is a precursor of an antitumor active agent, sarkomycin **8**.[5] Kinetic resolution of the racemic allylic alcohol derived from **5** by Sharpless epoxidation gave the optically active (*S*)-alcohol **6** (>99% ee).[11] Similar to racemate **1a**, the malonate (*S*)-**1a** prepared from **6** underwent iodocarbocyclization to give (*S*)-**2a**. Hydrolysis of the methyl ester group, decarboxylation, debenzylation and Swern oxidation gave optically active cyclosarkomycin **7**[5] in 63% overall yield from **6** [**7**, $[\alpha]_D$ -384° (c=1.67, CH_2Cl_2); lit.[5b] $[\alpha]_D$ -397° (c=2.00, CH_2Cl_2)].



[a] TrCl, Py (85%) [b] Ti(O*i*-Pr)$_4$, (-)-DCHT, *t*-BuOOH (30%) [c] BnBr, NaH then *p*-TsOH [d] MsCl, Et_3N then NaH, $CH_2(CO_2Me)_2$ [e] I_2, Ti(O*t*-Bu)$_4$, CuO [f] KOH then xylene, reflux [g] H_2, $Pd(OH)_2$ [h] Swern oxidation

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