Formal [4 + 1]- and [5 + 1]-Annulation by an SN2−Conjugate Addition Sequence: Stereoselective Synthesis of Highly Substituted Carbocycles
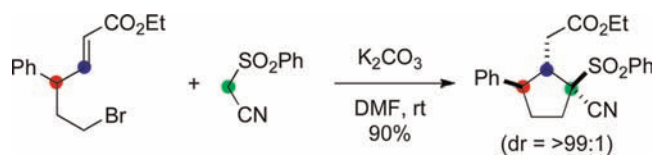
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ABSTRACT

K_2CO_3-mediated reactions of 6-bromo-2-hexenoates and 7-bromo-2-heptenoate with active methylene compounds deliver highly substituted cyclopentane and cyclohexane derivatives, respectively via a sequence of SN2−conjugate addition reactions (formal [4 + 1]- and [5 + 1]-annulation) in a diastereoselective manner.

Stereo- and regioselective construction of five- and six-membered carbocycles (cyclopentane and cyclohexane derivatives) is one of the most fundamental and important issues in synthetic organic chemistry because of the importance and prevalence of these motifs in many biologically active natural products and drug molecules.[1] Intermolecular annulation reactions allow for the rapid and selective construction of complex cyclic structures in a one-pot manner from relatively simple building blocks, which is

one of the most ideal processes in organic synthesis from atom-[2] and step-economical[3] points of view. While the annulation approaches to construct cyclopentane and cyclohexane derivatives have typically relied on the [3 + 2]-[4] and [4 + 2]-modes[5] (cycloaddition),[6] respectively, the corresponding [4 + 1]-[7] and [5 + 1]-processes[8] are scarce. Guided by these views as well as our current interest in conjugate addition reactions[9] of carbon nucleophiles

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toward acrylate derivatives,[10] we became interested in the base-mediated reaction of 6-halo-2-hexenoates and 7-halo-2-heptenoates with active methylene compounds that would provide cyclopentane and cyclohexane derivatives, respectively, via a sequence of S_N2–conjugate addition (a formal [4 + 1]- and [5 + 1]-annulation).[11−13] Herein, we report a study of this strategy on the carbocycle synthesis in terms of the reaction efficiency as well as the diastereoselectivity with various substituents.

We began our investigation by studying the K_2CO_3-mediated reactions of (E)-ethyl 4-benzyl-6-bromo-2-hexenoate (1a)[14] with a series of active methylene compounds 2 (Chart 1).[15] Malononitrile (2a), dimethylmalonate (2b) underwent smooth reactions in DMF at room temperature to afford trisubstituted-cyclopentanes 3aa and 3ab in good yields with high 2,3-trans-diastereoselectivity. The reaction of bis(phenylsulfonyl)methane (2c) was sluggish, giving cyclopentane 3ac only in 13% yield (in spite of excellent diastereoselectivity) even at a higher temperature of 60 °C. Three successive stereogenic centers were constructed on cyclopentane frameworks 3 using (phenylsulfonyl)acetonitrile (2d) and tert-butyl cyanoacetate (2e). The reaction with 2d provided a nearly single isomer of 3ad, while that of 2e dropped the diastereoselectivity of 3ae, where the stereochemistry of the major compound was 1,2-trans-2,3-trans. Interestingly, construction of a cyclohexane ring from (E)-ethyl 4-benzyl-7-bromo-2-heptenoate (1b) with malononitrile (2a) resulted in a reversal of diastereoselectivity that gave 2,3-cis-cyclohexane 3ba as a major product in good yield. However, the reaction of 1b with dimethyl malonate (2b) was very sluggish (70% yield, dr = 2.3:1 for 5 days), and that with (phenylsulfonyl)-acetonitrile (2d) gave three inseparable diastereomers

with low selectivity while the cyclization proceeded smoothly (93% yield for 24 h, dr = 39:36:25; see Supporting Information).

Chart 1. Synthesis of carbocycles by K_2CO_3-mediated reactions of 1 with active methylene compounds 2[a,b]
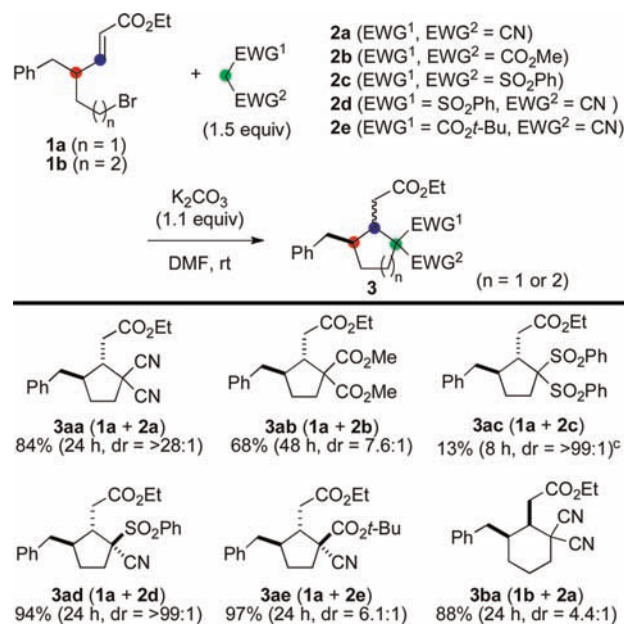
[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of 1 and 2 (1.5 equiv) with K_2CO_3 (1.1 equiv) in DMF (3 mL) at rt under a N_2 atmosphere. [b] Isolated yields were recorded above. Diastereomer ratio determined by ^{1}H NMR, and the structure of the major isomer shown. [c] The reaction was carried out at 60 °C. The acyclic product obtained only via the S_N2 reaction was isolated in 60% yield (see Supporting Information).

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(14) All the starting materials 1 used in this manuscript were prepared from the corresponding lactones as a racemic form; see Supporting Information for more details.

(15) Optimization of the reaction conditions for the present annulation was examined using (E)-ethyl 6-bromohex-2-enoate and (phenylsulfonyl)acetonitrile (2d), see Supporting Information.

Encouraged by the diastereoselective [4 + 1]-annulation to construct cyclopentane, we next set out to investigate the reaction of malononitrile (2a) with various 4-substituted 6-bromo-2-hexenoates (Table 1). Methyl (1c), methoxymethyl (1d), allylic (1e), propargylic (1f), isopropyl (1g), and phenyl (1h) moieties could be installed to afford the corresponding cyclopentanes in good to excellent chemical yields with high trans-diastereoselectivity.

The construction of cyclopentanes bearing three successive stereogenic centers was also examined using (phenylsulfonyl)acetonitrile (2d) with various (E)-ethyl 4-benzyl-6-bromo-2-hexenoates 1 (Table 2). The cyclopentanes 3 were obtained in good yields as a nearly single isomer except for the reactions of 1c and 1d (entries 1 and 2).

We next examined the effect of the substituents on the other positions of 6-bromo-2-hexenoates 1 for the diastereoselectivity (Schemes 1 and 2). Installation of a phenyl group on the C(5) position of 1i rendered the diastereoselectivity to be lower, giving trisubstituted cyclopentanes 3ia and 3ia′ in a 1.7:1 ratio (Scheme 1a). It was found that the reactions of trans-4,5-disubstituted 6-bromo-2-hexenoate 1j with 2a and 2d provided tetrasubstituted cyclopentanes 3ja and 3jd, respectively, in high diastereoselectivity

Table 1. Reactions with Malononitrile (**2a**)[a]

entry		R[1]	time/h	yield[b]	dr[c]
1	**1c**	Me	9	**3ca** (84%)	10:1
2	**1d**	MeO⌇	18	**3da** (94%)	12.1:1
3	**1e**	⌇	8	**3ea** (86%)	32:1
4	**1f**	⌇	21	**3fa** (86%)	35:1
5	**1g**	Me Me ⌇	14	**3ga** (75%)	35:1
6	**1h**	Ph	10	**3ha** (83%)	>99:1

[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of **1** and 1.5 equiv of **2** in DMF (3 mL) at rt under a N_2 atmosphere. [b] Isolated yields were recorded above. [c] The diastereomer ratio was determined by ^{1}H NMR.

**Table 2.** Reactions with (Phenylsulfonyl)acetonitrile (**2d**)[a]

entry		R[1]	time/h	yield[b]	dr[c]
1	**1c**	Me	23	**3cd** (73%)	8.8:1
2	**1d**	MeO⌇	18	**3dd** (89%)	15.7:1
3	**1e**	⌇	19	**3ed** (87%)	>99:1
4	**1f**	⌇	23	**3fd** (81%)	>99:1
5	**1g**	Me Me ⌇	14	**3gd** (78%)	>99:1
6	**1h**	Ph	24	**3hd** (92%)	>99:1

[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of **1** and 1.5 equiv of **2** in DMF (3 mL) at rt under a N_2 atmosphere. [b] Isolated yields were recorded above. [c] The diastereomer ratio was determined by ^{1}H NMR.

(Scheme 1b, c). These results implied that the diastereoselectivity of the present cyclization could be controlled mostly by the C(4) substituent.[16]

The reaction of (E)-ethyl 6-bromo-3-methylhex-2-enoate (**1k**) with **2a** delivered cyclopentane **3ka** bearing two successive quaternary carbon centers (Scheme 2a). Intrigued by whether the protonation process after the conjugate addition

(16) The diastereoselectivity of the cyclized product **3** was confirmed by the X-ray crystallographic analysis of several compounds as well as the NOE analysis of the corresponding lactone derivatives in Schemes 3 and 4. See Supporting Information for more details.

Scheme 1. Effects of the Position of Substituents
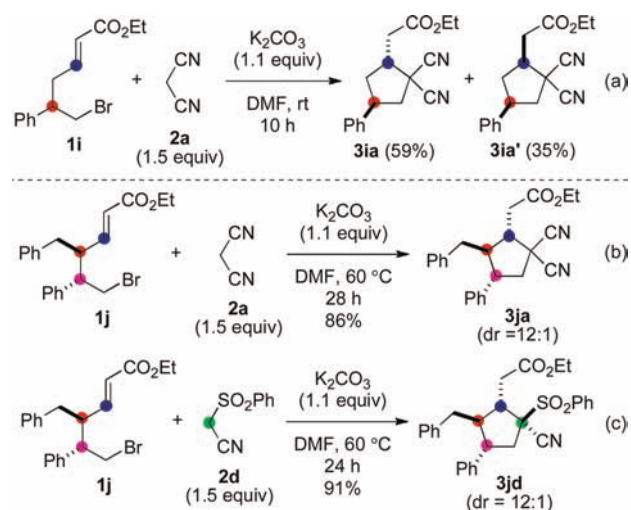
was selective,[17] (E)-ethyl 6-bromo-2-methylhex-2-enoate (**1l**) was subjected to the present reaction conditions with malononitrile (**2a**). The reaction afforded cyclopentane **3la** with good diastereoselectivity (7.7:1), where the (R*, R*)-isomer was formed as a major product probably via a concerted process of C–C bond formation and protonation (Scheme 2b; see Supporting Information for more details).[18]

Finally, further derivatization of the dicyanocyclopentanes and cyanophenylsulfonylcyclopentanes **3** was explored (Schemes 3 and 4). Dicyanocyclopentane **3aa** was treated with n-Bu$_3$SnH in the presence of a catalytic

Scheme 2. Reactions of **1k** and **1l**
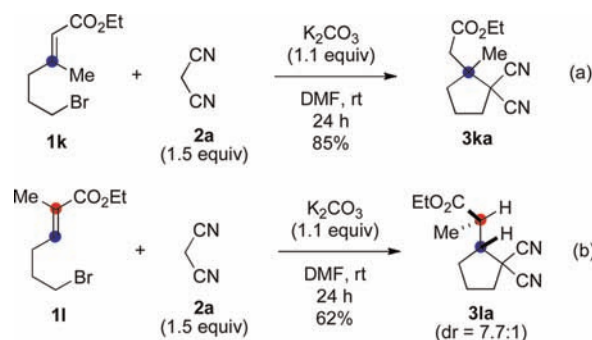
amount of AIBN, affording monodecyanated product **4aa**.[19] Chemoselective reduction of the ethoxycarbonyl

(17) For discussion of diastereoselective (enantioselective) protonation in conjugate addition of nucleophiles to acrylate derivatives, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. Nat. Chem. **2009**, 1, 359. (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. Tetrahedron: Asymmetry **2004**, 15, 3653. (c) Niu, D.; Zhao, K. J. Am. Chem. Soc. **1999**, 121, 2456.

(18) The stereochemistry of **3la** was determined by the NOE analysis of the corresponding lactone derivative **6la** prepared from **3la** via the procedures in Scheme 3.

(19) Curran, D. P.; Seong, C. M. Synlett **1991**, 107.

group of **4aa** by Kim's procedure[20] using the ate complex of DIBAL-H and *n*-BuLi gave alcohol **5aa**, which with aqueous acid treatment underwent lactonization, delivering *cis*-bicyclic lactone **6aa** in good yield (Scheme 3). The conversion of **3la** to lactone **6la** could lead to the confirmation of the stereochemical outcome by NOE measurement.

**Scheme 3.** Chemoselective Reduction−Lactonization of Dicyanocyclopentanes **3aa** and **3la**
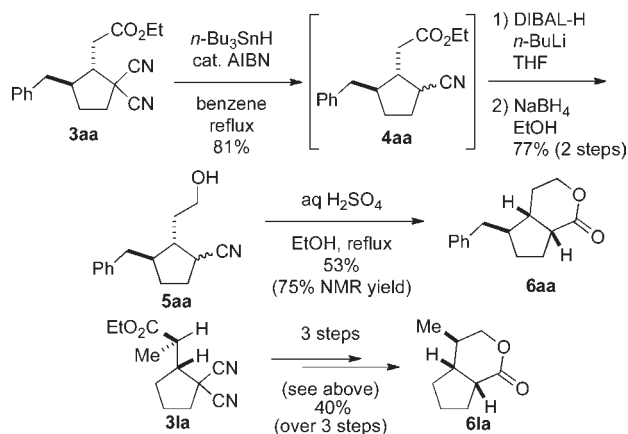
Kim's chemoselective reduction of the ethoxycarbonyl group of **3ad** and **3hd** followed by aqueous acid treatment gave α-sulfonyl bicyclic lactones **8ad** and **8hd**, respectively, in good yields. Reductive cleavage of the phenylsulfonyl group of **8** with lithium naphthalenide followed by protonation could afford *cis*-bicyclic lactone **6** smoothly with retention of the configuration. Similarly, the resulting lithium enolate generated from **8** could be trapped with carbon electrophiles such as methyl iodide and allyl bromide, giving **9ad** and **10ad** bearing a new quaternary carbon center with retention of the configuration.[21]

(20) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1217.

(21) The stereochemistry of **9ad** and **10ad** was determined by the NOE analysis, see Supporting Information.

(22) The preliminary discussion about the orign of the diastereoselectivity in the cyclization was described in Supporting Information.

Scheme 4. Chemoselective Reduction−Lactonization of Cyanophenylsulfonylcyclopentanes **3ad** and **3hd**
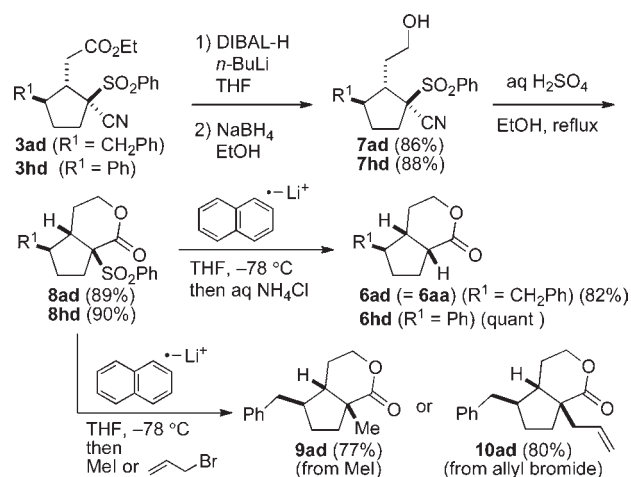
In summary, a concise and stereoselective methodology for the synthesis of highly substituted carbocycles has been developed.[22] Further investigation on the application of the present strategy to construct complex organic molecules is currently underway.

Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.