J|A|C|S ARTICLES

Published on Web 04/20/2009

Stereoselective Construction of Seven-Membered Rings with an All-Carbon Quaternary Center by Direct Tiffeneau−Demjanov-type Ring Expansion

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Abstract: Insertion of one methylene unit into the C−C bond of cyclohexanones is a potentially useful, straightforward method for the construction of seven-membered carbocycles. An especially appealing but largely unexplored method in this arena is the nucleophilic addition of diazoalkanes to the Lewis acid-activated cyclohexanones and subsequent ring expansion accompanied by the extrusion of nitrogen (direct Tiffeneau−Demjanov-type ring expansion). Our primary finding is the unprecedented insertion of α-alkyldiazoacetates to cyclohexanone and its heteroanalogues, generating seven-membered rings with one all-carbon quaternary center. On the basis of this finding, highly diastereoselective ring expansion of substituted cyclohexanones was developed, furnishing seven-membered rings with 1,4-quaternary-tertiary, 1,4-quaternary-quaternary, or 1,3,5-quaternary-tertiary-tertiary stereogenic centers in a single operation starting from readily available materials. The stereochemical outcome of the product can be easily predicted from the conformation of starting cyclohexanones. Enantioenriched products could be also accessed by the use of (−)-phenylmenthyl α-alkyldiazoacetates.

Introduction

Seven-membered carbocycles are found in a variety of natural products, and some of these compounds have attracted attention due to their prominent biological activities.[1] From the viewpoint of efficient target-oriented syntheses of these valuable molecules having a seven-membered ring and their congeners, as well as the diversity-oriented syntheses of seven-membered rings in search of yet-undiscovered chemotherapeutic lead compounds,[2] development of benign methods that allow us facile access to these fundamental carbocyclic units with complex functionalities and stereogenic centers is of great importance. In this vein, there have been various methods developed to date for the synthesis of seven-membered rings. Major synthetic maneuvers are the use of transition metal-catalyzed cycloadditions[3] and the use of ring-closing metathesis.[4] The other classical but underestimated strategy is the ring expansion of cyclohexanones, which does not require the use of expensive transition metals.[5] Lewis acid-catalyzed addition of diazoalkanes to cyclohexanones is recognized as one of these strategies.[6−8] The reaction proceeds via the addition of the nucleophilic diazomethine carbon to the Lewis acid activated carbonyl carbon to give the Tiffeneau−Demjanov rearrangement-like intermediate.[9] Subsequent rearrangement of the carbon skeleton with the extrusion of nitrogen furnishes the cycloheptanone. Despite the clear advantage of this process (we termed it direct Tiffeneau−Demjanov-type ring expansion), such as ready availability of starting materials, operational simplicity, and the use of benign Lewis acid

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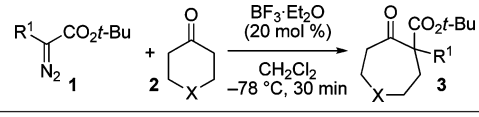
10.1021/ja900941k CCC: $40.75

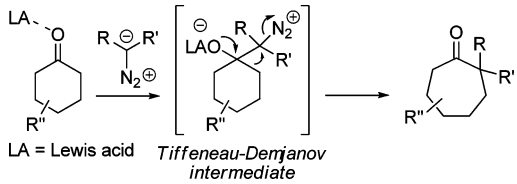
Table 1. Ring Expansion of Cyclohexanone and Its Heteroanalogues[a]



entry	R^1	X	% yield[b]
1	Bn	CH_2	80 (**3a**)
2	Me	CH_2	42 (**3b**)
3	*n*-Bu	CH_2	82 (**3c**)
4	*i*-Bu	CH_2	81 (**3d**)
5	Bn	O	73 (**3e**)
6	Bn	S	77 (**3f**)
7	Bn	NBoc	68 (**3g**)

[a] Reactions were performed with cyclohexanone (0.21 mmol) and α-substituted diazoacetate (0.20 mmol) in the presence of 20 mol % $BF_3 \cdot Et_2O$ (0.04 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yield.

catalysts, a complete lack of reliable procedures to introduce complex functionalities and stereogenic centers rigorously in thus-formed cycloheptanones severely limited its application in synthesis.

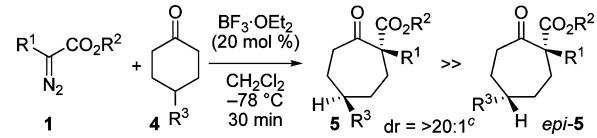


We report herein that the direct Tiffeneau−Demjanov-type ring expansion in conjunction with the use of α-alkyldiazoacetates[10] can be a promising tool for the expeditious synthesis of complex seven-membered rings having up to three stereogenic centers with one all-carbon quaternary center. Not only the carbocycles but other heterocycles including oxa-, aza-, and thiacycloheptanone analogues can be easily prepared using the same strategy. Furthermore, a simple chiral auxiliary-based approach allowed us a facile access to the enantioenriched seven-membered cycles.

Results and Discussion

We commenced this program from the investigation of the proper combination of Lewis acid and reaction conditions that realizes the unprecedented ring expansion of cyclohexanone with α-substituted diazoacetate. Gratifyingly, brief screening of Lewis acid catalysts in the ring expansion of cyclohexanone **2** (X = CH_2) with *t*-butyl α-benzyldiazoacetate **1** (R^1 = Bn) in CH_2Cl_2 at −78 °C identified $BF_3 \cdot Et_2O$ as a cheap and easy-to-handle catalyst of choice, giving the desired cycloheptanone **3a** with an all-carbon quaternary center in 80% yield (Table 1, entry 1). The scope of α-substituted diazoacetates was then investigated. Use of linear alkyl substituents such as methyl or *n*-butyl group was tolerated, giving the corresponding cycloheptanones **3b** and **3c** in 42% and 82% yield, respectively (entries 2 and 3). Concerning the α-diazoacetates bearing a branched alkyl group, the reaction of *t*-butyl α-isobutyldiazoacetate **1** (R^1 = *i*-Bu) proceeded smoothly (entry 4), although the use of *t*-butyl α-isopropyldiazoacetate **1** (R^1 = *i*-Pr) was found to be inapplicable. In this case, only the decomposition of diazoacetate was observed. The ring expansion of aryldiazoacetates was also found to be unproductive.

Table 2. Diastereoselective Ring Expansion of 4-Substituted Cyclohexanones[a]



entry	R^1	R^2	R^3	% yield[b]
1	Bn	*t*-Bu	*t*-Bu	91 (**5a**)
2	Bn	*t*-Bu	Me	64 (**5b**)
3	Bn	*t*-Bu	Ph	95 (**5c**)
4	Me	*t*-Bu	*t*-Bu	72 (**5d**)
5	Me	*t*-Bu	Ph	75 (**5e**)
6	Me	*t*-Bu	Me	61 (**5f**)
7	*n*-Bu	*t*-Bu	Me	60 (**5g**)
8	*i*-Bu	*t*-Bu	Me	40 (**5h**)
9	Bn	Me	*t*-Bu	83 (**5i**)
10	Bn	Me	Ph	79 (**5j**)
11	cinnamyl	*t*-Bu	*t*-Bu	54 (**5k**)
12	Bn	*t*-Bu	Nphth	69 (**5l**)

[a] Reactions were performed with cyclohexanone (0.21 mmol) and α-substituted diazoacetate (0.20 mmol) in the presence of 20 mol % $BF_3 \cdot Et_2O$ (0.04 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by the ^1H NMR of the crude reaction mixture.

We then moved our attention to the application in the ring expansion of 4-oxacyclohexanone **2** (X = O), which provides a seven-membered ring system incorporating an oxygen atom. As a result, the desired seven-membered heterocycle **3e** with one all-carbon quaternary center could be obtained uneventfully in 73% yield (entry 5). Utilization of thia- and azacyclohexanone in this reaction was also tolerated, giving the substituted thiepane **3f** in 77% yield and azepane **3g** in 68% yield (entries 6 and 7).

With the simple procedure for the synthesis of seven-membered rings bearing an all-carbon quaternary center in hand, we were particularly interested in the stereochemical relationship arising from the ring expansion of 4-substituted cyclohexanone **4** and α-alkyldiazoacetate (Table 2). At this point, our exploratory experiment using *t*-butyl α-benzyldiazoacetate **1** (R^1 = Bn) and 4-*t*-butylcyclohexanone **4** (R^3 = *t*-Bu) revealed that the ring expansion proceeded with the exclusive formation of the single isomer **5a**, thereby providing a novel means for the construction of a carbon framework with remote 1,4-tertiary-quaternary stereocenters (entry 1). The relative stereochemistry of the major product **5a** was assigned unambiguously by X-ray crystallographic analysis as benzyl and *t*-butyl groups oriented in a cis-fashion.[11] The broad scope of this reaction became immediately obvious. Concerning the 4-substituent of cyclohexanone, small alkyl and aromatic groups were both tolerated (entries 2 and 3). No substantial difference in diastereoselectivity was observed irrespective of the alkyl substituent of diazoacetate (entries 4−8). Additionally, use of *t*-butyl ester was found not to be indispensable, because use of methyl ester also provided the corresponding cycloheptanones **5i** and **5j** with high diastereoselectivity (entries 9 and 10). An allylic moiety can be incorporated into the ring system by the use of α-cinnamyldiazoacetate, which would secure the further elaboration of the product (entry 11). Use of 4-(*N*-phthaloylamino)cyclohexanone **4** (R^3 = Nphth) gave rise to the cycloheptanone **5l** with a nitrogen functionality (entry 12).

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(11) For the determination of stereochemical relationships, see the Supporting Information.

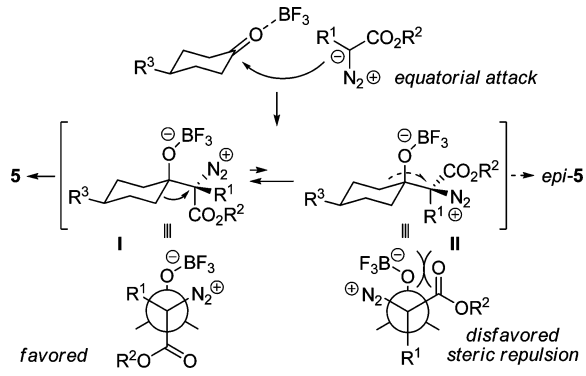


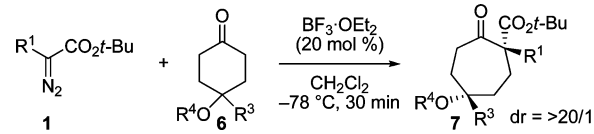
Figure 1. Explanation on the stereochemical outcome of direct Tiffeneau−Demjanov-type ring expansion.

As for the mechanistic aspect, it is considered that the electronegative diazomethine carbon of α-alkyldiazoacetate attacks the carbonyl carbon of 4-substituted cyclohexanone from the equatorial orientation of the chair conformer. Accordingly, the initial step of this ring expansion is assumed to be the formation of diazonium intermediate as shown in Figure 1. At this stage, the remote stereochemical relationship between the carbon center bearing 4-substituent of cyclohexanone and diazomethine carbon center is transferred to the issue of from which rotamer, **I** or **II**, the alkyl group migrates. It can be envisaged that the rotamer **I** will be formed preferentially to avoid the larger steric bulk between the borate moiety and the ester moiety as compared to that of the primary alkyl group. The following rearrangement then provides the cycloheptanone with the observed stereochemistry.

This mechanistic inspection led us to the next assumption that cyclohexanones bearing a siloxy or alkoxy group as 4-substituent would be converted in the opposite sense of diastereoselection, because the siloxy and alkoxy group attached to the 4-position of cyclohexanone are known to favor the axial orientation due to the electrostatic interaction between the nonbonding orbital of the oxygen moiety and π*-orbital of the carbonyl group.[12] Based on this premise, the ring expansion of 4-*t*-butyldimethylsiloxycyclohexanone **6** (R^3 = H, R^4 = TBS) and *t*-butyl α-benzyldiazoacetate **1** (R^1 = Bn) was investigated under conditions identical to those above (Table 3). As expected, the ring expansion provided the cycloheptanone **7a** projecting the benzyl group and the siloxy group in a trans-fashion (entry 1). The reaction also has generality concerning the α-substituent of the diazoacetate (entry 2). Additionally, use of 4-benzyloxycyclohexanone **6** (R^3 = H, R^4 = Bn) was also tolerant, giving the desired cycloheptanone **7c** in 86% yield (entry 3).

The successful implementation of stereoselective ring expansions of 4-alkyl and 4-siloxy cyclohexanones demonstrated above reminded us of the simple extension wherein cyclohexanones having both an alkyl group and a siloxy group at 4-position in an equatorial and axial way, respectively, are utilized. It is expected that the stereoselective ring expansion would provide the cycloheptanone with remote 1,4-quaternary-quaternary stereocenters consisting of one all-carbon quaternary center and one tertiary alcohol. The ring expansion of 4-methyl-4-trimethylsiloxycyclohexanone **6** (R^3 = CH_3, R^4 = TMS) with *t*-butyl α-benzyldiazoacetate **1** (R^1 = Bn) provided the cycloheptanone **7d** in 66% yield with the rigorous control of diastereoselectivity (entry 4). The ring expansion proceeded irrespective of 4-alkyl substituent of cyclohexanone or α-substituent of diazoacetate, giving a series of cycloheptanones **7e**−**7h** in the range of 62−79% yield (entries 5−8).

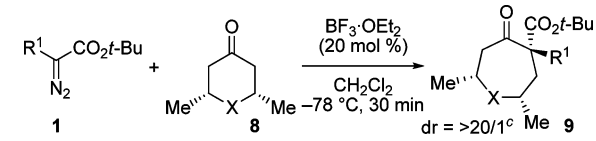
Table 3. Diastereoselective Ring Expansion of 4-Siloxy-, 4-Alkoxy-, and 4-Alkyl-4-siloxy Cyclohexanones[a]



entry	R^1	R^3	R^4	% yield[b]
1	Bn	H	TBS	93 (**7a**)
2	Me	H	TBS	69 (**7b**)
3	Me	H	Bn	86 (**7c**)
4	Bn	Me	TMS	66 (**7d**)
5	Me	Me	TMS	62 (**7e**)
6	*n*-Bu	Me	TMS	79 (**7f**)
7	Me	*n*-Pr	TMS	67 (**7g**)
8	Me	Bn	TMS	66 (**7h**)

[a] Reactions were performed with cyclohexanone (0.21 mmol) and α-substituted diazoacetate (0.20 mmol) in the presence of 20 mol % BF_3·Et_2O (0.04 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by the ^{1}H NMR of the crude reaction mixture.

Table 4. Diastereoselective Ring Expansion of *cis*-3,5-Dimethylcyclohexanone and Its Oxa-analogue[a]



entry	R^1	X	% yield[b]
1	Bn	CH_2	78 (**9a**)
2	Me	CH_2	61 (**9b**)
3	*n*-Bu	CH_2	71 (**9c**)
4	Bn	O	91 (**9d**)
5	Me	O	50 (**9e**)
6	*n*-Bu	O	84 (**9f**)

[a] Reactions were performed with cyclohexanone (0.21 mmol) and α-substituted diazoacetate (0.20 mmol) in the presence of 20 mol % BF_3·Et_2O (0.04 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by the ^{1}H NMR of the crude reaction mixture.

Thus far, we had focused on the ring expansion of 4-substituted cyclohexanones, which generates seven-membered rings bearing substituents with a 1,4-stereochemical relationship. To further broaden the utility of this diastereoselective ring expansion, we selected *cis*-3,5-dimethylcyclohexanone **8** (X = CH_2) as a model substrate, which would furnish a seven-membered ring with 1,3,5-quaternary-tertiary-tertiary stereogenic centers (Table 4). Because such cyclohexanone exists as a chair conformer projecting two methyl groups in equatorial orientation, it can be envisaged that the ring expansion of this material would provide the cycloheptanone bearing the alkyl group derived from the alkyldiazoacetate and two methyl groups of the cyclohexanone in trans-relationship. Actually, the ring expansion of *cis*-3,5-dimethylcyclohexanone with α-benzyldiazoacetate gave the cycloheptanone **9a** with the anticipated stereochemical relationship as a single isomer in 78% yield (entry 1). As in the case of other cyclohexanones, this ring expansion has generality concerning the α-substituent of diazoacetate (entries 2 and 3).

As exemplified in Table 1, one great advantage of the protocol developed herein is the simple access to the heteroanalogues

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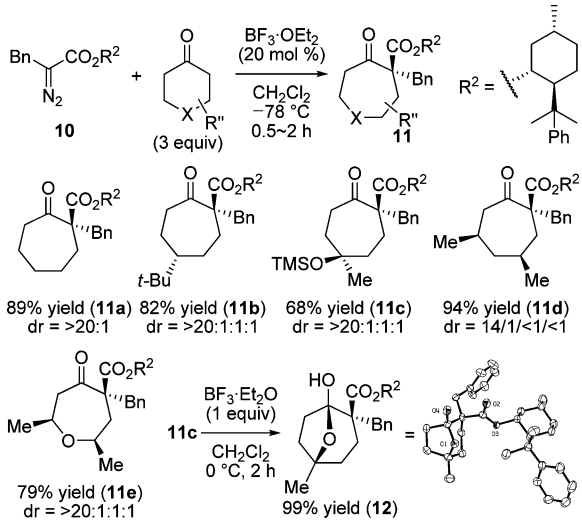
Scheme 1. Asymmetric Ring Expansion of Cyclohexanones with (−)-Phenylmenthyl α-Benzyldiazoacetate

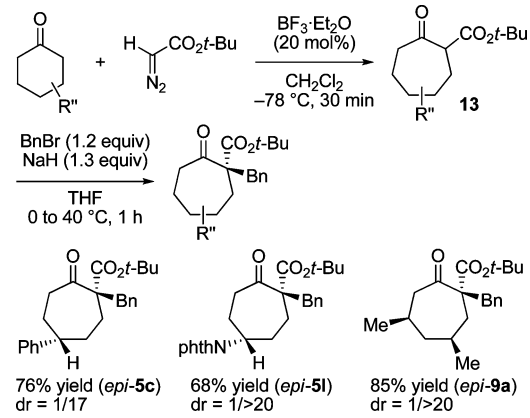


using the same tactics as in the synthesis of carbocycles. To highlight this point, we investigated the ring expansion of 4-oxa-*cis*-3,5-dimethylcyclohexanone **8** (X = O) with α-alkyldiazoacetates, which would generate oxepane rings having stereogenic centers at the ethereal carbon. As expected, the desired compounds **9d**−**9f** were obtained uneventfully in 50−91% yields as a single isomer (entries 4−6).

To further underline the synthetic power of this diastereoselective ring expansion, we introduced the α-benzyldiazoacetate having the (−)-phenylmenthyl ester **10** in this reaction system to realize asymmetric variant,[10b] which is expected to give seven-membered rings with one enantioenriched all-carbon quaternary center[13] and additional one or two remote stereogenic centers (Scheme 1). To our great delight, the initial attempt using the combination of cyclohexanone and (−)-phenylmenthyl α-benzyldiazoacetate **10** furnished the seven-membered carbocycle **11a** with an excellent level of diasterecontrol, thus successfully introducing an enantioenriched all-carbon quaternary center in the ring system. Essentially single isomer was observed in every reaction employing other cyclohexanone derivatives (**11b**−**11e**), although longer reaction time was required presumably due to the steric hindrance of the phenylmenthyl moiety. In all cases, an excess amount of cyclohexanone or its derivatives was utilized to maximize the yield based on the rather precious diazoacetate **10**.

The additional notion of this diastereoselective construction of cycloheptanones is the complementary relationship between

Scheme 2. Preferential Formation of the Opposite Diastereomer via the Ring Expansion−Alkylation Sequence Using α-Unsubstituted Diazoacetate



our protocol and the ring expansion−alkylation sequence using cycloheptanone and α-unsubstituted diazoacetate (Scheme 2). For example, the ring expansion of 4-phenylcyclohexanone with *t*-butyl α-benzyldiazoacetate furnished the seven-membered ring **13** (R″ = Ph at C5) with an acidic α-hydrogen. Benzylation of this material by the conventional approach predominantly provided the compound *epi*-**5c** (see Table 2, entry 3) projecting the benzyl and phenyl groups in a trans-fashion with high diastereoselectivity. In the case of 4-siloxycyclohexanones (see Table 3), this ring expansion−alkylation sequence furnished the products with only low to moderate selectivity (data not shown).

In conclusion, we disclosed a reliable and predictable method for the stereoselective construction of functionalized seven-membered rings with an all carbon quaternary stereocenter.[14] The strategy described herein could be successfully transferred to the asymmetric variants by the use of chiral auxiliary-based approach.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. Y.N. thanks the Japan Society for the Promotion of Science for Young Scientists for Research Fellowships.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA900941K

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