ORGANIC LETTERS

2012
Vol. 14, No. 23
6048–6051

Novel Skeleton Transformation Reaction of α-Pyrone Derivatives to Spirobicyclo[3.1.0]hexane Derivatives Using Dimethylsulfoxonium Methylide

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Received October 25, 2012

ABSTRACT

By applying a skeleton transformation reaction using dimethylsulfoxonium methylide, a novel reaction was identified by which 5,6,7,8-tetrahydrocoumarin with the electron-withdrawing group at C3 was led to the spirobicyclo[3.1.0]hexane-cyclohexane derivative. Moreover, by establishing the scope of this reaction, it was confirmed that it is possible to apply this reaction to not only ring-fused α-pyrone derivatives but also alkyl-chain-substituted α-pyrone derivatives in moderate to good yields.

The skeleton transformation reaction with domino C−C bond formation and cleavage to generate products possessing different skeletons from a substrate is an attractive tool in synthetic organic chemistry for the construction of the basic skeleton in the target molecule. We previously reported on a novel skeleton transformation reaction of coumarin derivatives **1** having an electron-withdrawing group at C3 to 2-substituted cyclopenta[*b*]benzofuran-3-ol derivatives **2** by treatment with more than 2 equiv of dimethylsulfoxonium methylide, which is Corey's sulfur ylide used in Corey−Chaykovsky cyclopropanation[1] (Scheme 1).[2] This reaction proceeds through the ring-opening reactivity derived from the strain of cyclopropane formed in the Corey−Chaykovsky reaction. We accomplished the total syntheses of natural products, namely, linderol A[3] and adunctin B,[4] with the construction of their basic skeleton by this transformation reaction.[5,6]

Herein, we describe a novel skeleton transformation reaction, which affords 2-oxo-spirobicyclo[3.1.0]hexane

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(2) (a) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 5603. (b) Yamashita, M.; Okuyama, K.; Kawajiri, T.; Takada, A.; Inagaki, Y.; Nakano, H.; Tomiyama, M.; Ohnaka, A.; Terayama, I.; Kawasaki, I.; Ohta, S. *Tetrahedron* **2002**, *58*, 1497.

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(4) Arimitsu, K.; Nomura, S.; Iwasaki, H.; Ozeki, M.; Yamashita, M. *Tetrahedron Lett.* **2011**, *52*, 7046.

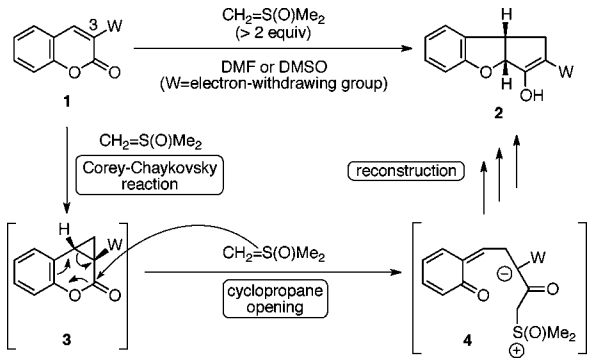
(5) Our group also reported the improvement of the skeleton transformation reaction using dimethylsulfoxonium methylide, which transformed 1,2a-disubstituted 1,2,2a,8b-tetrahydro-3*H*-benzo[*b*]cyclobuta[*d*]pyran-3-ones to *r*-1,*t*-4a,*t*-9b-1,3-disubstituted 1,2,4a,9b-tetrahydrodibenzofuran-4-ols.

(6) For references of our synthesis study with the improved skeleton transformation reaction, see: (a) Yamashita, M.; Inaba, T.; Shimizu, T.; Kawasaki, I.; Ohta, S. *Synlett* **2004**, 1897. (b) Yamashita, M.; Shimizu, T.; Kawasaki, I.; Ohta, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2315. (c) Yamashita, M.; Shimizu, T.; Inaba, T.; Takada, A.; Takao, I.; Kawasaki, I.; Ohta, S. *Heterocycles* **2005**, *65*, 1099. (d) Yamashita, M.; Inaba, T.; Nagahama, M.; Shimizu, T.; Kosaka, S.; Kawasaki, I.; Ohta, S. *Org. Biomol. Chem.* **2005**, *3*, 2296. (e) Yamashita, M.; Yadav, N. D.; Sawaki, T.; Takao, I.; Kawasaki, I.; Sugimoto, Y.; Miyatake, A.; Murai, K.; Takahara, A.; Kurume, A.; Ohta, S. *J. Org. Chem.* **2007**, *72*, 5697. (f) Yamashita, M.; Yadav, N. D.; Sumida, Y.; Kawasaki, I.; Kurume, A.; Ohta, S. *Tetrahedron Lett.* **2007**, *48*, 5619. (g) Yadav, N. D.; Yamashita, M.; Nagahama, M.; Inaba, T.; Sawaki, T.; Kawasaki, I.; Kurume, A.; Ohta, S. *Tetrahedron Lett.* **2008**, *49*, 1627. (h) Nomura, S.; Arimitsu, K.; Yamaguchi, S.; Kosuga, Y.; Kakimoto, Y.; Komai, T.; Hasegawa, K.; Nakanishi, A.; Miyoshi, T.; Iwasaki, H.; Ozeki, M.; Kawasaki, I.; Kurume, A.; Ohta, S.; Yamashita, M. *Chem. Pharm. Bull.* **2012**, *60*, 94.

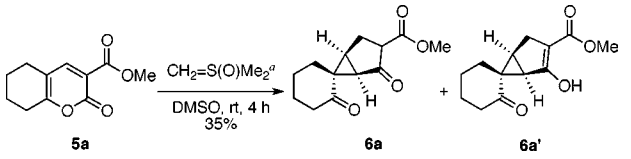
10.1021/ol302942m
Published on Web 11/19/2012

derivatives from α-pyrone-3-carboxylate derivatives, using dimethylsulfoxonium methylide. The development of this method for the synthesis of spirocyclic cyclopropane is an interesting challenge in synthetic and medicinal chemistry owing to the characteristic structure and reactivity of this cyclopropane.[7] Additionally, because of the highly conformationally constrained effect of cyclopropane, bicyclo[3.1.0]-hexane is also a useful structure for medicinal chemistry.[8,9] To the best of our knowledge, the methodology for the synthesis of such a ring system has been limited to date.[8,10]

Scheme 1. Skeleton Transformation Reaction of Coumarin Derivative (Our Previous Work)



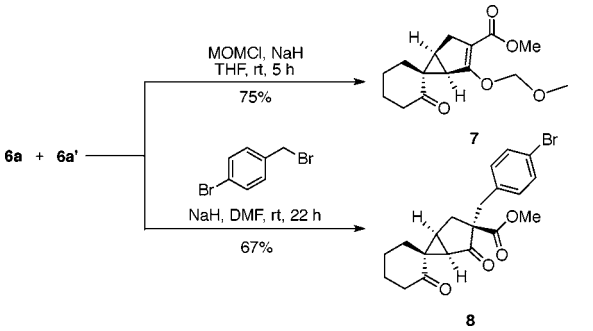
Scheme 2. Transformation Reaction of 5,6,7,8-Tetrahydrocoumarin Derivative (This Work)[a]



[a] Prepared using $Me_3S(O)I$ (2.4 equiv) and NaH (2.0 equiv).

We were interested in the reactivity of dimethylsulfoxonium methylide against 5,6,7,8-tetrahydrocoumarin **5a** possessing the methyl ester moiety as the electron-withdrawing group at C3 (Scheme 2). The starting material **5a** was easily prepared as described in the literature,[11] that is, condensation and cyclization reaction between cyclohexanone and dimethyl methoxymethylenemalonate with LDA in THF. By treating **5a** with the *in situ* prepared dimethylsulfoxonium methylide from 2.4 equiv of trimethylsulfoxonium iodide and 2.0 equiv of NaH in DMSO,[12] we obtained the novel product with 35% yield.

Scheme 3. Derivatization of **6a** for Structure Determination



The molecular formula of the product was found to be $C_{13}H_{16}O_4$ by HRMS, but it was difficult to determine the structure of the product from ^1H and ^{13}C NMR spectral data because they were very complex for analysis. We assumed that this complexity of NMR data was due to the equilibrium of keto−enol tautomers derived from the β-ketoester moiety of the product. Therefore, to simplify the NMR data, the methoxymethyl (MOM) group was introduced to the enol moiety of the product (Scheme 3). The resulting protection of the enol moiety by the MOM group enabled us to determine the products of the skeleton transformation reaction as keto−enol tautomers of **6a** and **6a′**, which are spirocyclic cyclopropane derivatives with the bicyclo[3.1.0]hexane structure, by analysis of the spectral data of **7** from ^1H NMR, ^{13}C NMR, HMQC, and HMBC (Figure 1). Finally, the structure and stereochemistry of **6a** and **6a′** were confirmed as methyl (1*R**,1′*R**,5*S**)-2,2′-dioxospiro[bicyclo[3.1.0]hexane-6,1′-cyclohexane]-3-carboxylate and its enol tautomer by X-ray crystallographic analysis of the *p*-bromobenzyl derivative **8** (Figure 2). This outcome encouraged us to study this unique reaction in detail.

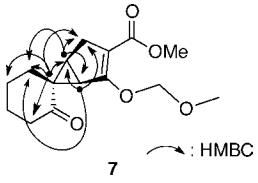


Figure 1. Selected HMBC in **7**.

First, we started to explore the optimal conditions. The conditions were optimized by modifying the amounts of

(7) Takasu, K.; Nagamoto, Y.; Takemoto, Y. *Chem, Eur. J.* **2010**, *16*, 8427.

(8) Boatman, P. D.; Schrader, T. O.; Kasem, M.; Johnson, B. R.; Skinner, P. J.; Jung, J. K.; Xu, J.; Cherrier, M. C.; Webb, P. J.; Semple, G.; Sage, C. R.; Knudsen, J.; Chen, R.; Taggart, A. K.; Carballo-Jane, E.; Richman, J. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2797.

(9) Monn, J. A.; Massey, S. M.; Valli, M. J.; Henry, S. S.; Stephenson, G. A.; Bures, M.; Herin, M.; Catlow, J.; Giera, D.; Wright, R. A.; Johson, B. G.; Andis, S. L.; Kingston, A.; Schoepp, D. D. *J. Med. Chem.* **2007**, *50*, 233.

(10) Vash, D.; Hung, H. H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911.

(11) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033.

(12) **Procedure for *in situ* preparation of dimethylsulfoxonium methylide:** Trimethylsulfoxonium iodide was added in one portion to a suspension of NaH (60% in mineral oil) in DMSO at rt, and the mixture was stirred for 30 min under N_2.

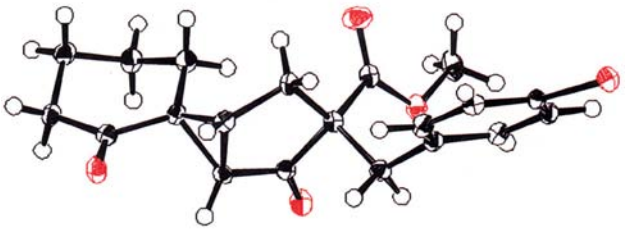
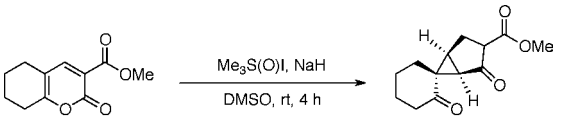


Figure 2. ORTEP drawing of **8**.

Table 1. Optimization of Reaction Conditions



5a **6a**

entry	$Me_3S(O)I$ (equiv)	NaH (equiv)	yield[a]
1	2.4	2.0	35%
2	3.0	2.5	44%
3	3.8	3.2	73%
4	4.8	4.0	61%
5	5.0	4.0	34%

[a] Isolated yield of a mixture of keto–enol tautomers.

Table 2. Effect of Ester Moiety on Transformation Reaction

5 **6**

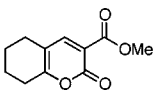
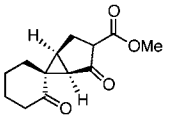
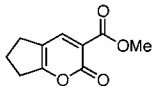
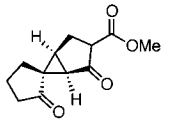
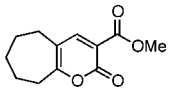
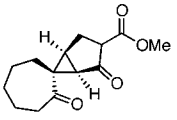
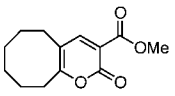
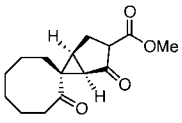
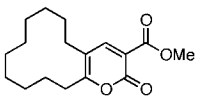
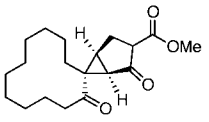
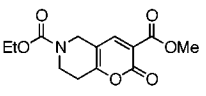
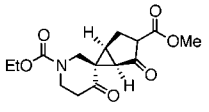
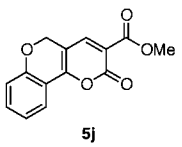
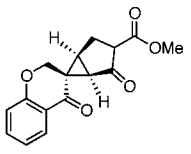
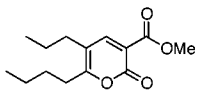
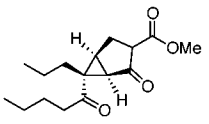
entry	R, **5**	time (h)	yield in **6**[a]
1	Me, **5a**	4	**6a**, 73%
2	Et, **5b**	4	**6b**, 59%
3	*tert*-Bu, **5c**	4	**6c**, 43%
4	benzyl, **5d**	24	**6d**, 34%

[a] Structures were determined by transformation to the corresponding MOM-protected enol derivatives.[13] Isolated yield of a mixture of keto–enol tautomers.

reagents, both trimethylsulfoxonium iodide and NaH, as shown in Table 1. Under the conditions of entry 3, dimethylsulfoxonium methylide was prepared from 3.8 equiv of trimethylsulfoxonium iodide and 3.2 equiv of NaH; the yield of the keto–enol tautomers of **6a** was improved from 35% to 73%, as compared with the yield of entry 1.

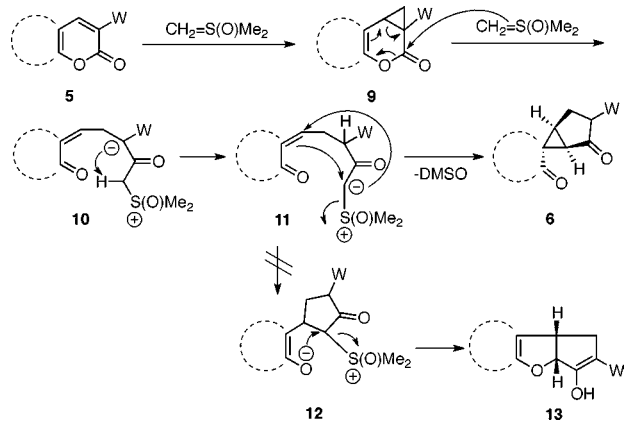
Next, under the optimized conditions (Table 1, entry 3), we examined the effect of the ester moiety at C3 of the starting material on this transformation reaction (Table 2). However, no improvement was observed in the case of ethyl, *tert*-butyl, and benzyl ester derivatives **5b**–**d**, as compared with the case of the methyl ester derivative **5a**. Regarding the reaction of **5d**, a benzyl ester derivative, the product yield was the lowest and it took a longer time to complete the reaction than in the case of other ester derivatives. This finding revealed that the larger the ester moiety at C3 is, the lower the yield of the product is. It was considered that a small and electron-poor substituent would be suitable for this reaction as an electron-withdrawing group at C3.

Table 3. Application to α-Pyrone Derivative

entry	substrate	product[a]	yield[b]
1	 **5a**	 **6a**	73%
2	 **5e**	 **6e**	75%
3	 **5f**	 **6f**	76%
4	 **5g**	 **6g**	62%
5	 **5h**	 **6h**	43%
6	 **5i**	 **6i**	44%
7	 **5j**		58%
8	 **5k**	 **6k**	42%

[a] Structures were determined by transformation to the corresponding MOM-protected enol derivatives.[13] [b] Isolated yield of a mixture of keto–enol tautomers.

Scheme 4. Plausible Reaction Mechanism



We proposed that this unique transformation reaction would be applied to not only 5,6,7,8-tetrahydrocoumarin **5a**, which is a six-membered ring-fused α-pyrone derivative, but also other substituted α-pyrone derivatives. Under the optimal conditions established, the scope of this transformation reaction was explored against various ring-fused α-pyrone derivatives and alkyl-chain-substituted α-pyrone derivatives possessing an electron-withdrawing group at C3 (Table 3). For all cases, the structures of products were determined from the spectral data of compounds that were prepared by introducing the MOM group to the *β*-ketoester moiety on the right side of the isolated products in order to suppress the keto−enol tautomerism, and the stereochemistry of the products was speculated from **6a**.[13] As expected, with the transformation reaction, five-, seven-, and eight-membered ring-fused α-pyrone derivatives **5e**−**g**[14] were successfully converted to corresponding spirobicyclo[3.1.0]hexane products **6e**−**g** in relatively good yields, namely, 75%, 76%, and 62%, respectively (entries 2−4). Moreover, the application to macrocyclic ring-fused α-pyrone derivative **5h** gave the corresponding product **6h** with a moderate yield (entry 5). In entries 6 and 7, heterocycle fused compounds **5i**,[14] **j** were transformed to the spiro[bicyclo[3.1.0]hexane-piperidine] derivative **6i** and spiro[bicyclo[3.1.0]hexane-chroman] derivative **6j** with moderate yields. Furthermore, in the case of a ring-unfused substrate, an α-pyrone derivative **5k** substituted with alkyl chains, an *n*-propyl group at C5, and an *n*-butyl group at C6,[15] the reaction proceeded to give bicyclo[3.1.0]hexane **6k** having the 1-pentanone substituent and *n*-propyl tether at C6.

The plausible mechanism of this reaction is illustrated in Scheme 4. After cyclopropane intermediate **9** was formed via the Corey−Chaykovsky reaction, the cyclopropane ring would be opened by the attack of the additional CH_2=S(O)Me_2 to give the ring-opening intermediate **10** similarly to the skeleton transformation reaction against coumarin derivatives.[2b] Migration of the acidic proton occurs, followed by the addition of the produced sulfur ylide portion to the *β*-carbon in the α,*β*-unsaturated carbonyl moiety. The attack of the obtained α-carbanion and elimination of DMSO would immediately lead to the bicyclo[3.1.0]hexane product without formation of the enol intermediate **12** because of the lack of the conjugated ring system as in the coumarin derivatives.[2b,16] The stereochemistry at the spirocenter of **6** would be controlled by steric hindrance between the carbonyl group on the left side and the cyclopentane ring during formation of the spirobicyclichexane moiety as shown in **6**.

In summary, we have described a novel skeleton transformation reaction from α-pyrone derivatives possessing an ester group as the electron-withdrawing group at C3 to bicyclo[3.1.0]hexane compounds with good to moderate yields. This reaction is interesting from the viewpoint of obtaining products containing potentially reactive cyclopropane moieties, which indicates that such products would become useful intermediates for organic synthesis. Details about the research and further applications of this reaction will be reported in due course.

Acknowledgment. This research was supported in part by a Strategic Research Foundation Grant-Aided Project for Private Universities from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (MEXT), a Grant-in-Aid for Scientific Research (C) (22590023) from Japan Society for the Promotion of Science (JSPS), and the Kyoto Pharmaceutical University Fund for the Promotion of the Scientific Research. We are very grateful to Ms. S. Fujioka in our laboratory for assistance in synthesis.

Supporting Information Available. Experimental procedures, spectral data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and crystal information files (CIF) for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) The spectral data of MOM-protected enol derivatives are shown in the Supporting Information.

(14) Schotten, T.; Janowski, F.; Schmidt, A.; Hinrichsen, K.; Ammenn, J. *Synthesis* **2003**, 2027.

(15) Ceglia, S. S.; Kress, M. H.; Nelson, T. D.; McNamara, J. M. *Tetrahedron Lett*. **2005**, *46*, 1731.

(16) In the case of entries 5 and 8 in Table 3, products corresponding to **13** were obtained with 19% yield from **5h** and a trace amount from **5k**.

The authors declare no competing financial interest.