ORGANIC LETTERS

2010
Vol. 12, No. 21
4984−4987

Asymmetric Synthesis of 2,3-Dihydro-4-pyranones by Reaction of Chiral 3-Alkoxycyclobutanone and Aldehydes

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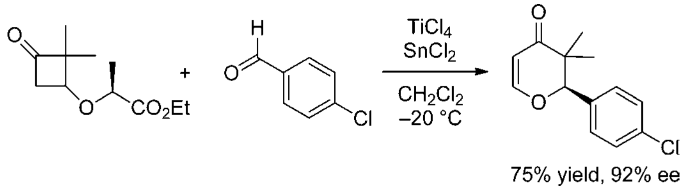
Received September 8, 2010

ABSTRACT



Chiral cyclobutanone which had ethyl L-lactate as a chiral auxiliary at the 3-position reacted with aldehydes to give 2,3-dihydro-4-pyranones in up to 93% ee by combined use of titanium(IV) chloride and tin(II) chloride.

Chiral pyrans are versatile building blocks for the synthesis of many biologically active compounds, such as pheromones, antitumor agents, and terpenoids.[1] Chiral dihydropyranones **1** (Figure 1, R^1, R^2 = H) have been prepared by enantioselective hetero-Diels−Alder (HDA) reactions[2] between siloxydienes and aldehydes by using various chiral Lewis acid catalysts such as BINOL−metal (Mg,[3a] Ti,[3b] Zn,[3c] or Al[3d]) complexes, Cu(II)[4a] or Rh(II)[4b] carboxamidates, and salen−metal (Cr(III) or Mn(III)) complexes.[5a−c] Chiral organocatalysts[6] such as TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol),[7a,b] BAMOL (1,1′-biaryl-2,2′-dimethanol),[7c] or oxazolines,[7d] which activate aldehydes through hydrogen bonds, have also promoted enantioselective HDA reactions between 1-amino-3-siloxy-1,3-butadienes[8] and al-

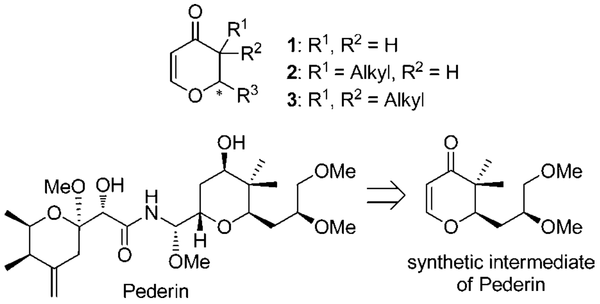


Figure 1. 2,3-Dihydro-4-pyranones (**1**−**3**) and synthetic intermediate of pederin.

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(1) Smith, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675.

(2) For a representative review on the asymmetric HDA reaction, see: Jørgensen, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

(3) (a) Du, H.; Zhang, X.; Wang, Z.; Bao, H.; You, T.; Ding, K. *Eur. J. Org. Chem.* **2008**, 2248. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (c) Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

(4) (a) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. (b) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366.

(5) (a) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) Berkessel, A.; Vogl, N. *Eur. J. Org. Chem.* **2006**, 5029. (c) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845.

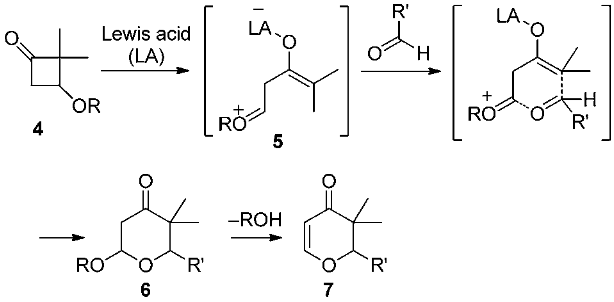
(6) Recent review: Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1.

10.1021/ol1021355 © 2010 American Chemical Society
Published on Web 10/05/2010

dehydes. Synthesis of dihydropyranones **2** bearing alkyl groups at their 3-position (R^1 = alkyl, R^2 = H) is more difficult, and only a few methods have been reported for their preparation by using dirhodium(II) chiral carboxamidate[9a] catalysts, Cu(II) bisoxazoline,[9b] or BINOL−metal (Al[3d] or Zr[9c]) complexes. Chiral dihydropyranones **3** having dialkyl groups at their 3-position are seen in the structure of natural products such as the pederin family of natural products.[10] However, preparation of chiral dihydropyranones **3** needs many steps which include asymmetric aldol reaction.[11a,b]

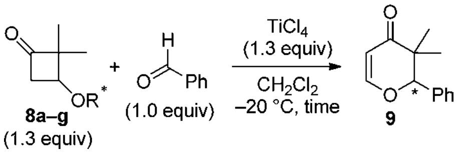
We have reported a Lewis acid-catalyzed reaction between 3-alkoxycyclobutanones **4** and aldehydes[12] to afford various types of 2,3-dihydro-4-pyranones **7** (Scheme 1). A zwitterionic intermediate **5** was generated by Lewis acid-catalyzed ring opening of 3-alkoxycyclobutanone **4**. Compound **6** was formed by reaction of **5** and aldehyde, and elimination of alcohol from adduct **6** gave dihydro-4-pyranone **7**. It was then thought that introducing a chiral auxiliary into the 3-alkoxy group of cyclobutanone **4**[13] would give chiral dihydropyranone **7**.

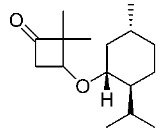
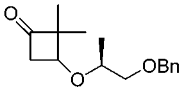
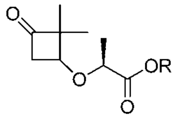
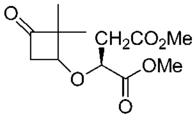
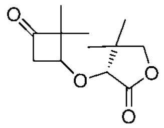
Scheme 1. Lewis Acid-Catalyzed Reaction between Cyclobutanone **4** and Aldehyde to Dihydropyranone **7**



First, screening for an effective chiral auxiliary for asymmetric induction between 3-alkoxycyclobutanone **4** and aldehyde was carried out by reaction between cyclobutanone **8a**−**g** and benzaldehyde in the presence of titanium(IV) chloride (Table 1). Reaction of cyclobutanones **8a** and **8b**, which were prepared from (−)-menthol and (*S*)-1-(benzoxy)-propane-2-ol, respectively, gave dihydro-4-pyranone **9** in low ee's (7−3% ee, entries 1 and 2). Moderate to good asymmetric induction was observed in the reaction of cyclobutanones **8c**−**e**, which were derived from L-lactic esters (44−79% ee, entries 3−5). The reaction of cyclobutanones **8f** and **8g**, which were prepared from L-malic acid dimethyl ester and D-pantolactone, afforded cycloadduct **9** in 58% and 19% ee, respectively (entries 6 and 7). Therefore, L-ethyl lactate was chosen as a chiral auxiliary for the present asymmetric reaction.

Table 1. Effect of Chiral Auxiliary on Diastereoselective Cycloaddition between Cyclobutanone **8a**−**g** and Benzaldehyde



entry	cyclobutanone[a]	time (h)	yield (%)[b]	% ee[c]
1	 **8a**	0.5	42	7 (*S*)
2	 **8b**	5.0	43	3 (*S*)
3	 **8c**: R = Et	3.0	60	79 (*R*)
4	**8d**: R = ^{i}Pr	8.0	73	77 (*R*)
5	**8e**: R = $(CH_2)_7CH_3$	8.0	43	44 (*R*)
6[d]	 **8f**	55.0	43	58 (*R*)
7	 **8g**	30.0	67	19 (*S*)

[a] Diastereomer ratios: **8a** (49:51), **8b** (45:55), **8c** (60:40), **8d** (36:64), **8e** (31:69), **8f** (36:64), **8g** (15:85). [b] Isolated yield. [c] Determined by chiral HPLC. For the absolute configuration, see the text. [d] The reaction was carried out at −20 to 0 °C.

The chiral cyclobutanone **8c** was prepared from L-ethyl lactate in three steps (Scheme 2). 1-Ethoxyethyl ether of L-ethyl lactate **10** was prepared in 92% yield by reaction of L-ethyl lactate and ethyl vinyl ether in the presence of a catalytic amount of TFA. Treating **10** with triethylamine and TMSOTf gave vinyl ether **11** (79% yield).[14] [2 + 2]

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(7) (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (b) Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749. (c) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336. (d) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.

(8) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321.

(9) (a) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665. (b) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. (c) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1221.

(10) Piel, J.; Butzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S. *J. Nat. Prod.* **2005**, *68*, 472.

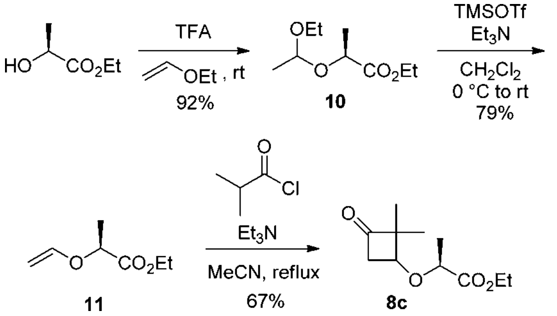
(11) (a) Brown, L. E.; Landaverry, Y. R.; Davies, J. R.; Milinkevich, K. A.; Ast, S.; Carlson, J. S.; Oliver, A. G.; Konopelski, J. P. *J. Org. Chem.* **2009**, *74*, 5405. (b) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357.

(12) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600.

(13) (a) Darses, B.; Greene, A. E.; Coote, S. C.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 821. (b) Delair, P.; Kanazawa, A. M.; de Azevedo, M. B. M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707.

(14) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653.

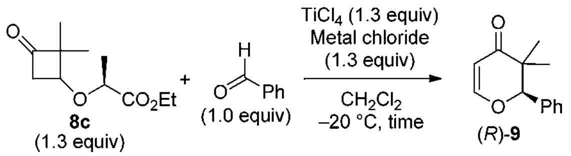
Scheme 2. Preparation of Cyclobutanone **8c**



Cycloaddition by using vinyl ether **11**, isobutyryl chloride, and triethylamine afforded cyclobutanone **8c** in 67% yield as a mixture of two diastereomers (60:40).

Interestingly, it was proven that addition of some metal chlorides in a titanium(IV) chloride-promoted asymmetric reaction between **8c** and benzaldeyde improved the enantioselectivity of product **9** (Table 2). The use of copper(II) chloride and zinc(II) chloride slightly improved the ee of adduct **9**, but yields were decreased (entries 2 and 3). Among the metal chlorides tested, the use of tin(II) chloride gave **9** in 70% yield with the best enantioselectivity (88% ee, entry 4). The role of tin(II) chloride in this reaction has not yet been clarified. The use of each separated diastereomer of **8c** gave almost the same results as those obtained by employing a mixture of two diastereomers of **8c**.

Table 2. Effect of Metal Chloride on Diastereoselective Cycloaddition between Chiral Cyclobutanone **8c** and Benzaldehyde

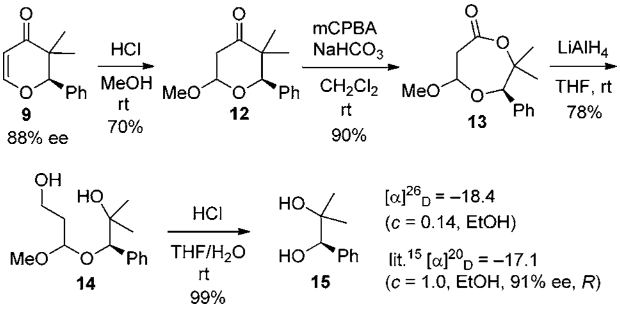


entry	metal chloride	time (h)	yield (%)[a]	% ee[b]
1	none	3.0	60	79
2	$CuCl_2$	6.0	26	81
3	$ZnCl_2$	1.5	58	83
4	$SnCl_2$	8.0	70	88

[a] Isolated yield. [b] Determined by chiral HPLC.

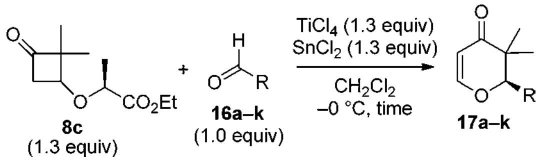
The absolute configuration of **9** was determined by comparison with the specific rotation of known diol **15**[15] (Scheme 3). Baeyer–Villiger oxidation of **12**, which was prepared by reaction of compound **9** (88% ee) with methanolic hydrogen chloride,[16] gave lactone **13** in 90% yield. Reduction of **13** with lithium aluminum hydride gave diol **14** in 78% yield, and hydrolysis of **14** gave diol **15** in 99% yield. The specific rotation of obtained **15** ($[\alpha]^{26}_{D} = -18.4$) suggested that its absolute configuration was *R*.[15]

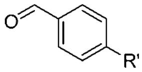
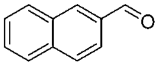
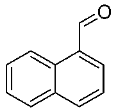
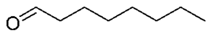
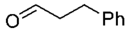
Scheme 3. Determination of the Absolute Configuration of **9**



Next, the scope and limitations of diastereoselective reaction of **8c** were investigated by using various aldehydes (Table 3). When electron-withdrawing groups were substituted at the para-position of the phenyl group of benzaldehyde **16a**–**e**, the corresponding 2,3-dihydropyranones **17a**–**e** were obtained in good yields (64–78%) and with high ee's

Table 3. Diastereoselective Cycloaddition with Various Aromatic Aldehydes



entry	aldehyde	time (h)	yield (%)[a]	% ee[b]
1	 R' = CF_3 (**16a**)	12.5	68	89
2	R' = F (**16b**)	10.0	67	91
3	R' = Cl (**16c**)	8.0	75	92
4	R' = Br (**16d**)	12.0	64	90
5	R' = I (**16e**)	12.5	78	88
6	R' = Me (**16f**)	8.0	59	77
7	R' = Ph (**16g**)	11.5	70	77
8	 (**16h**)	5.0	60	93
9	 (**16i**)	6.0	58	75
10	 (**16j**)	10	43	78
11	 (**16k**)	6.5	47	76

[a] Isolated yield. [b] Determined by chiral HPLC analysis. The absolute configuration was deduced from compound (*R*)-**9**.

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(15) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L.; Raghavan, K. V. *J. Am. Chem. Soc.* **2001**, *123*, 9220.

(16) Mori, K.; Mori, H. *Tetrahedron* **1987**, *43*, 4097.

(88−92% ee, entries 1−5). On the other hand, aldehydes bearing a methyl or phenyl group at the para-position of the phenyl group gave lower ee's (77% ee, entries 6 and 7). In comparison with 2-naphthylaldehyde **16h**, which gave cycloadduct **17h** in 60% yield and 93% ee (entry 9), the reaction with 1-naphthylaldehyde **16i** gave the desired adduct **17i** in a lower yield (58%) and with lower ee's (75% ee, entry 10). These results suggest that this reaction was influenced by steric effects. Reactions between **8c** and aliphatic aldehydes **16j** and **16k** gave the desired products **17j** and **17k** in moderate yields (43% and 47%) and with good ee's (76% and 78% ee, entries 10 and 11).

In summary, chiral 2,3-dihydro-4-pyranones were prepared by a diastereoselective asymmetric reaction of aldehyde and 3-alkoxycyclobutanone bearing L-ethyl lactate as a chiral auxiliary. It is expected that these chiral cyclobutanones will be effective for other reactions with imines,[17] allylsilanes,[18] and silyl enol ethers[19] to afford the corresponding chiral dihydropyranones and cyclohexanones.

Acknowledgment. This work was supported by a Grant from Suntory Institute for Bioorganic Research and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266.

(18) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822.

(19) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831.