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Carbohydrates as chiral auxiliaries in enantioselective synthesis of four stereoisomers of optically active α,γ-substituted γ-butyrolactones

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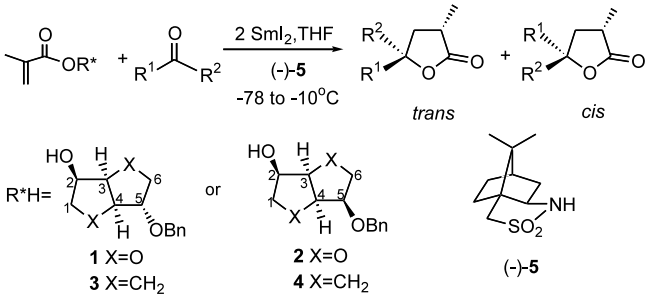
Abstract—Using several easily accessed and inexpensive chiral auxiliaries derived from carbohydrates, all four stereoisomers of the optically active α,γ-substituted γ-butyrolactones were obtained respectively in high enantiomeric purities (up to 96% ee for *trans* and up to >99% ee for *cis*) by the SmI_2-induced reductive coupling reaction in the presence of a proton source.

Optically active γ-butyrolactones and their derivatives have attracted much attention in recent years due to their broad occurrence in biologically active natural products and their use as important intermediates for the synthesis of natural products, fine chemicals and pharmaceuticals.[1] Among the increasing number of methods, the approach based on SmI_2-mediated reductive radical reactions reported by Fukuzawa and coworkers[2] is one of the effective methods for preparing chiral γ-butyrolactones, and we[3] have also developed a highly enantioselective synthesis of α,γ-substituted γ-butyrolactones based on SmI_2-induced reductive coupling reaction, in which the isosorbide derivative **1** or the isomannide derivative **2** was employed as the chiral auxiliary and high ee values were obtained (Scheme 1).



Scheme 1.

Further investigation of this coupling reaction in our group indicated that the presence of oxygen atoms (or at least one oxygen atom) in the auxiliary skeleton is required for the induction of high enantioselectivities for the formation of lactones. Thus, when compounds **3** or **4**, with similar structures[4] to **1** or **2** but without an oxygen atom in the bisfused tetrahydronfuran rings, were used as the auxiliary the ee values decreased.[5] In view of that a samarium atom is an oxyphilic atom having over six coordinating sites, and that carbohydrates are easily accessible and inexpensive natural products in which multi-functional groups, stereogenic centers and oxygen atoms are mounted within one molecule,[6] we turned our attention to the use of the derivatives generated from carbohydrates other than **1** and **2** in the SmI_2-reductive coupling reaction.

Herein, we wish to report that all four stereoisomers of the optically active α,γ-substituted γ-butyrolactones can be obtained in high diastereoselectivity and enantiomeric purity by using carbohydrates based chiral auxiliaries, respectively, via the SmI_2-induced reductive coupling reaction.

First, we synthesized auxiliaries **6** and *ent*-**6** from commercially available D-fructose and L-sorbose, respectively (Fig. 1).[7] Then they were treated with methacryloyl chloride in the presence of Et_3N in CH_2Cl_2 to provide the corresponding α,β-unsaturated esters. The examination of the reaction of these two chiral α,β-unsaturated esters with several ketones was performed by using TrOH (triphenylmethanol) and (1*S*)-(−)-2,10-camphorsultam [(−)-**5**] as sterically hin-

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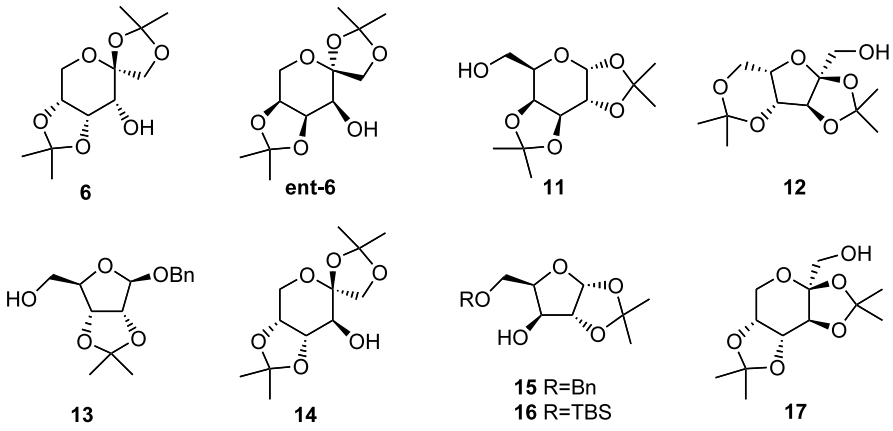
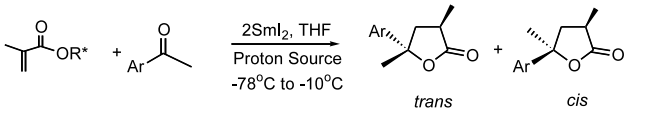


Figure 1.

dered proton source (Scheme 2).[8] The results are listed in Table 1.

It is delightful that among these tested auxiliaries and ketones some gave satisfactory results in both diastereoselectivities and enantioselectivities. It is different from our previous work that the *cis* products were obtained as major products and the ee values of *cis* products were excellent. For example, when **6** was used as a chiral auxiliary, high diastereoselectivity (*trans*/*cis*=4/96) was obtained, and the *cis* product was formed as the major product in 97% enantiomeric



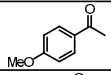
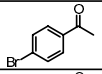
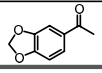
7 Ar=naphthy; **8** Ar=*p*-MeO-C_6H_4; **9** Ar=*p*-Br-C_6H_4;
10 Ar=3,4-methylenedioxy-phenyl

Scheme 2.

excess (entry 1). Accordingly, *ent*-**6** (it is the enantiomer of the chiral auxiliary **6** and was readily prepared from L-sorbose)[7b] was used as a chiral auxiliary, afford an equally high diastereoselectivity (*trans*/*cis*=7/93) and enantioselectivity (93% ee) for the synthesis of α,γ-substituted γ-butyrolactone (entry 4 in Table 1). As such, we were able to prepare two optically active isomers (−)-*cis*-**7** and (+)-*cis*-**7** in high ee values when compounds **6** and *ent*-**6** were employed as chiral auxiliaries, respectively. Additionally, when (−)-**5** or (+)-**5** was used as proton source, the diastereoselectivity and enantiomeric purity were still in high manner (entries 2, 3, 5, and 6 in Table 1). And the stereochemistry of *cis* product was dominated by the configuration of chiral auxiliary. It is suggested that the chelation of the samarium atom with the oxygen atoms in the chiral auxiliary **6** and *ent*-**6** played an important role in the enantioselective induction.

As shown in Table 1, the ee values (99 and >99%) were achieved with 4′-bromoacetophenone (entries 8 and 9),

Table 1. Synthesis of high optically active α,γ-substituted γ-butyrolactone in Scheme 2

Entry	R*-H	Ketone	Product	Proton Source	*trans*/*cis*[a]	*ee*%[b] (*trans*)	*ee*%[b] (*cis*)	yield%[c]	$[\alpha]_D$ sign (*cis*)
1	**6**		**7**	TrOH	4/**96**	72	**97**	68	(-)
2	**6**		**7**	**(-)-5**	3/**97**	-[d]	**98**	75	(-)
3	**6**		**7**	**(+)-5**	2/**98**	26	**92**	67	(-)
4	**ent-6**		**7**	TrOH	7/**93**	52	**93**	67	(+)
5	**ent-6**		**7**	**(-)-5**	3/**97**	-[d]	**92**	65	(+)
6	**ent-6**		**7**	**(+)-5**	4/**96**	33	**97**	60	(+)
7	**6**		**8**	**(-)-5**	13/87	14	77	62	(+)
8	**6**		**9**	**(-)-5**	3/**97**	-[d]	**99**	59	(+)
9	**ent-6**		**9**	**(+)-5**	1/**99**	-[d]	**>99**	65	(-)
10	**6**		**10**	**(-)-5**	40/60	89	85	58	(+)

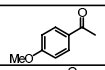
[a]*Trans* and *cis* configuration were confirmed by ^{1}H-^{1}H NOESY in light of their NOE effect, and the ratio of *trans*/*cis* were determined by HPLC.

[b]The *ee* values were determined by HPLC analysis on chiralcel OJ, OD, AD column [detected at 254nm].

[c]Total isolated yield of *trans* and *cis* products.

[d]Not detected.

Table 2. Synthesis of optically active 2,4-dimethyl-4-aryl-γ-butyrolactone used new chiral auxiliaries in Scheme 2[a]

Entry	R*-H	Ketone	Product	*trans*/*cis*[b]	*ee*%[c] (*trans*)	*ee*%[c] (*cis*)	Yield%[d]	$[\alpha]_D$ sign (*trans*)
1	**11**		**7**	70/30	63	24	83	(+)
2	**12**		**7**	57/43	79	51	63	(+)
3	**13**		**7**	69/31	68	43	83	(+)
4	**14**		**7**	70/30	**92**	81	21	(+)
5	**15**		**7**	63/37	64	8	76	(+)
6	**16**		**7**	72/28	61	44	50	(+)
7	**17**		**7**	71/29	**92**	66	79	(+)
8	**17 (TrOH)**		**7**	70/30	53	31	75	(+)
9	**17 [(+)-5]**		**7**	50/50	25	37	73	(+)
10	**17**		**8**	73/27	**90**	8	89	(-)
11	**17**		**9**	73/27	**93**	34	52	(-)
12	**17**		**10**	72/28	**90**	31	73	(-)

[a](-)-**5** was used as proton source except entries 8 and 9.

[b]*Trans* and *cis* configuration were confirmed by ^{1}H-^{1}H NOESY in light of their NOE effect, and the ratio of *trans*/*cis* were determined by HPLC.

[c]The *ee* values were determined by HPLC analysis on chiralcel OJ, OD, AD column [detected at 254nm].

[d]Total isolated yield of *trans* and *cis* products.

the enantiopure products (+)-*cis*-**9** and (−)-*cis*-**9** were obtained simply by recrystallization. The absolute configuration of (−)-*cis*-**9** [given in entry 9 using *ent*-**6** and (+)-**5**] and (+)-*cis*-**9** [given in entry 8 using **6** and (−)-**5**] were determined as (2*R*,4*R*) and (2*S*,4*S*) by X-ray diffraction.[9] And it was also found that the chiral proton sources (−)-**5** and (+)-**5** used in the reaction can be recovered quantitatively (>95% recovery in the case of entries 2, 3, 5 and 6) and be reused without diminishing the enantioselectivity.

The success in the synthesis of two new *cis* isomers (entries 1, 4, 6 and 9 in Table 1) of highly optically active α,γ-substituted γ-butyrolactones prompted us to find other new chiral auxiliaries for the preparation of *trans* isomers. Therefore, we prepared as many auxiliaries as possible, such as **11**–**17**, from commercially available carbohydrates (Fig. 1).[10] Then, these chiral auxiliaries were treated accordingly with methacryloyl chloride in the presence of Et_3N in CH_2Cl_2 to provide the chiral α,β-unsaturated esters. Examinations were carried out by using these new auxiliaries with 2′-acetonaphthone in the presence of (−)-**5** as the proton source under the optimized conditions.[8] Table 2 summarizes the results, indicating that the formation of *trans* isomers were predominated in all cases, with *trans*/*cis* ratios up to 72/28. The *trans* isomer was obtained with good to excellent enantioselectivity in most cases. For example, when **14** and **17** (both prepared from D-fructose) were employed as chiral auxiliaries, the *trans*-**7** was obtained with excellent ee value (92%, entries 4 and 7), the only difference is that the yield given by **14** is 21%. TrOH and (+)-**5** were also examined as proton source, but the results were not as good as (−)-**5** given.[11] The chiral auxiliary **17** was used successfully again for the highly enantioselective synthesis of *trans* lactones **8**–**10**, implying a broad substrate scope.

The absolute configuration of *trans* product was determined as (2*R*,4*S*) by X-ray analysis of the single crystal of *trans*-**9**.[9] Since (2*S*,4*R*)-*trans*-**9** has already been prepared and reported in our previous papers.[3a,b] Thus, two isomers of *cis*-**9** and two isomers of *trans*-**9** have been prepared in our hands.

In summary, we have reported a facile and effective method for the synthesis of α,γ-substituted γ-butyrolactones. All four stereoisomers of α,γ-substituted γ-butyrolactones represented by **9** can be prepared in high enantiopurity based on different chiral auxialiaries derived from carbohydrates. Notably, high diastereoselectivities and ee values of the major product (*cis*-product) were achieved. Further investigation on the double asymmetric induction and the mechanistic explanation of this reaction are in progress.

Acknowledgements

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References

1. (a) Katoh, T.; Nishide, K.; Node, M.; Orura, H. *Heterocycles* **1999**, *50*, 833; (b) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385.
2. Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.
3. (a) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953; (b) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229; (c) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773.

4. Compounds **3** and **4** were prepared from 1,5-cyclooctadiene according to the following literature: (a) Henry, P. M.; Davies, M.; Ferguson, G.; Philips, S.; Restivo, R. *J. Chem. Soc., Chem. Commun.* **1974**, 112; (b) Lemke, K.; Ballschuh, S.; Kunath, A.; Theil, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2051.
5. When we used **3** and **4** as chiral auxiliaries under the same conditions, the ee values of *trans*-**7** were 48 and 66%, respectively. The mechanistic study on the reaction will be published elsewhere.
6. Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336.
7. **6** from D-fructose: (a) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133. *ent*-**6** from L-fructose which was derived from L-sorbose: (b) Chen, C.-C.; Whistler, R. L. *Carbohydr. Res.* **1988**, *175*, 265.
8. *General procedure for the SmI_2-mediated asymmetric reductive coupling reaction for the preparation of chiral α,γ-substituted γ-butyrolactones*. To Sm metal powder 230 mg (1.5 mmol) in a Schlenk flask was added a solution of diiodomethane (freshly distilled, 0.081 mL, 1.0 mmol) in THF (5 mL) at room temperature under nitrogen. After approximately 1 h, the color of the mixture solution turned to deep blue, indicating the formation of samarium diiodide. The solution was then cooled to −78°C, and a mixture of α-methacrylate (0.5 mmol), ketone (0.5 mmol), and proton source (0.5 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 2 h at the same temperature and allowed to warm slowly, the reaction was subsequently quenched at −10°C with 5% aqueous HCl, extracted with diethyl ether, washed with aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was finally purified by flash-column chromatography on silica gel to afford the optically active γ-butyrolactones and recovered chiral proton source. Due to the easy preparation, the chiral auxiliaries have not been recovered in our procedure. The general characterization data of *trans*-**7**, *cis*-**7**, *trans*-**8**, *cis*-**8**, *trans*-**9**, *cis*-**9**, *trans*-**10**, *cis*-**10** have been published in Ref. 3a.
Determination of the enantiomeric excess. The enantiomeric excess was determined by HPLC analysis on chiralcel OJ, AD, OD column (detected at 254 nm; eluent: *n*-hexane/*iso*-propyl alcohol). For comparison, racemic γ-butyrolactones were prepared by the reaction of methyl methacrylate, with corresponding ketones in the presence of *tert*-butyl alcohol.
9. Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre, CCDC Nos. 204432, 204433 and 204434 for (2*S*,4*R*)-*trans*-**9**, (2*S*,4*S*)-*cis*-**9** and (2*R*,4*R*)-*cis*-**9**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. **12** from D-galactose: (a) Martins Alho, M. A.; D'Accorso. N. B.; Thiel, I. M. E. *J. Heterocyclic Chem.* **1996**, *33*, 1339. **13** from L-sorbose: (b) Van Grunenberg, H.; Bredt, C.; Freudenberg, W. *J. Am. Chem. Soc.* **1938**, *60*, 1507. **14** from D-ribose: (c) Duvold, T.; Francis, G. W.; Papaioannou, D. *Tetrahedron Lett.* **1995**, *36*, 3153. **15** from D-fructose: (d) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. **16** and **17** from D-xylose: (e) Enholm, E. J.; Gallagher, M. E.; Jiang, S.; Batson, W. A. *Org. Lett.* **2000**, *2*, 3355; (f) Lu, Y.-X.; Just, G. *Tetrahedron* **2001**, *57*, 1677. **18** from D-fructose: (g) Koßmehl, G.; Volkheimer, J. *Liebigs Ann. Chem.* **1989**, 1127.
11. The possibility of preparing chiral γ-butyrolactone via double asymmetric induction employing both a chiral auxiliary and a chiral proton source will be published elsewhere.