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Tetrahedron Letters 44 (2003) 745–749

TETRAHEDRON LETTERS

Enantiodivergent syntheses of γ-substituted butenolides with tertiary and quaternary asymmetric centers

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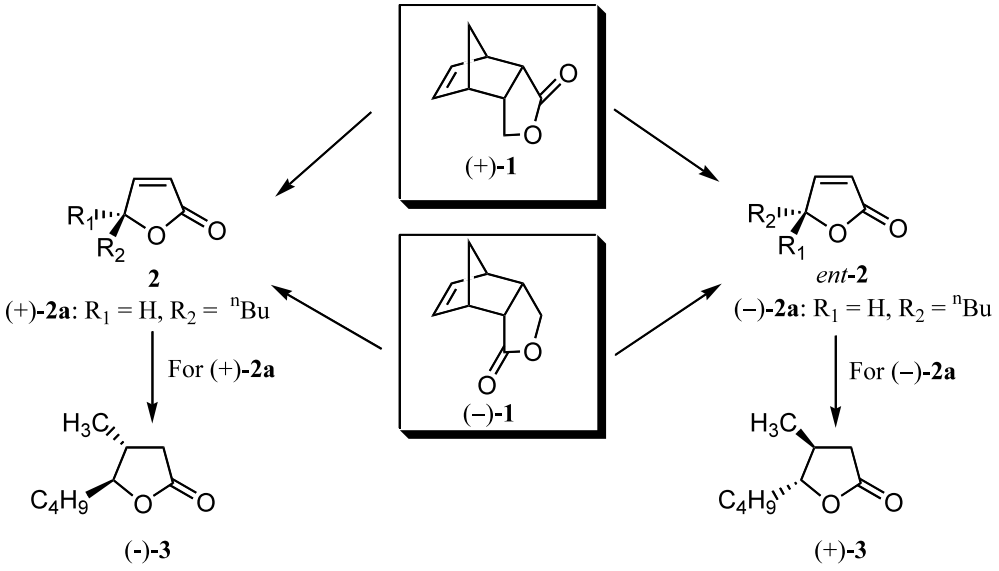
Received 18 October 2002; revised 13 November 2002; accepted 22 November 2002

Abstract—Continuous nucleophilic addition with several organometallic reagents to tricyclic lactone (−)-**1** proceeded diastereoselectively. Newly generated tertiary and quaternary asymmetric centers were controlled by the order in which the nucleophilic reagents were added. Using this methodology, enantiodivergent syntheses of several γ-substituted butenolides with tertiary and quaternary asymmetric centers were established from a single chiral material.

Chiral γ-substituted butenolides **2** are known to be useful synthons for the enantiocontrolled construction of a variety of biologically active natural and unnatural compounds.[1] Therefore, chiral synthesis of γ-substituted butenolides has been an ongoing challenge for researchers attempting the organic synthesis of certain substances.[2,3] We have recently reported the enantiodivergent synthesis of (+)- and (−)-*trans*-quercus lactones **3** from (+)-**1** as a single chiral material via continuous diastereoselective nucleophilic addition.[4] We have found that (+)-**1** is the synthetic equivalent of both enantiomers of chiral γ-butyl-substituted butenolide **2a** (Scheme 1). We report here an application of this methodology to synthesize both enantiomers of several chiral γ-substituted butenolides **2** with tertiary and quaternary asymmetric centers from a single chiral material **1** (Scheme 1).[5]



Scheme 1.

Keywords: chiral synthesis; chiral building block; nucleophilic addition; lactones; butenolides.

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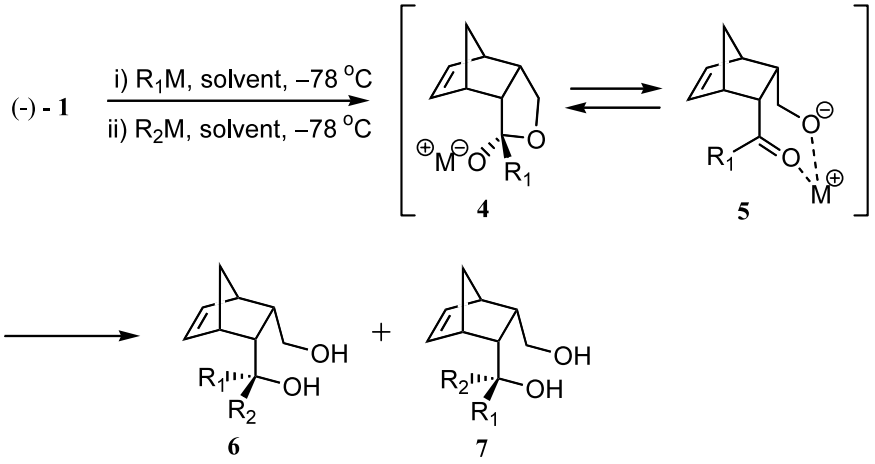
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02711-9

In the present study optically pure tricyclic lactone (−)-**1**, prepared from dicyclopentadiene by our established method,[6] was allowed to react with the first organometallic reagent (R_1M), and then continuously reacted with the second organometallic reagents (R_2M) in the same flask to furnish diastereomeric diols **6** and **7** (Scheme 2). The results of this continuous nucleophilic addition are summarized in Table 1. In the case of using diisobutylaluminum hydride (DIBAL) as the first nucleophilic reagent (R_1M) and using some organometallic reagents as the second nucleophilic reagents (R_2M) in tetrahydrofuran (THF), diastereoselective nucleophilic addition proceeded preferentially to yield diol **6** with some alkyl and aryl substitutions, and to selectively construct a tertiary asymmetric center (entries 1, 2, 6, and 8). In comparison with entries 1 and 2, a higher yield and higher diastereoselectivity of diols **6a** and **7a** were observed, when *n*butylmagnesium chloride (*n*BuMgCl) was used as R_2M. These results suggested that it was suitable for the reaction to use Grignard reagent as R_2M. For this reason, we demonstrated the use of some other Grignard reagents as R_2M (entries 6 and 8). We then inverted the newly generated asymmetric center in the order in which the nucleophilic reagents were added. In THF, lactone (−)-**1** reacted with stoichiometric amounts of *n*butyllithium (*n*BuLi) as R_1M to avoid dialkylation,[7] and continuously reacted with DIBAL or L-Selectride as R_2M. In these cases, a lower yield and lower diastereoselectivity of diols **6b**, **7b** were observed (entries 3 and 4). When toluene was used as a solvent, a drastic improvement in this reaction was observed.[8] Entry 5 shows that diol **6b** was obtained in 78% yield as an almost single product, and that the inversion of the newly generated tertiary asymmetric center succeeded. Although a similar result was obtained in the case of the methyl group (entry 7),



Scheme 2.

Table 1. Continuous nucleophilic addition to lactone (−)-**1**

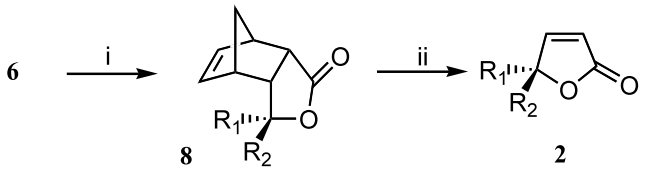
Entry	Solvent	R_1M	R_2M	Products	Yield[a] (%)	Ratio[b] **6**:**7**
				6 and **7**		
1	THF	DIBAL	*n*BuLi	**a**: R_1=H, R_2=*n*Bu[c]	46	71:29
2	THF	DIBAL	*n*BuMgCl	**a**: R_1=H, R_2=*n*Bu	81	>99:1
3	THF	*n*BuLi	DIBAL	**b**: R_1=*n*Bu, R_2=H	38	52:48
4	THF	*n*BuLi	L-Selectride	**b**: R_1=*n*Bu, R_2=H	26	67:33
5	Toluene	*n*BuLi	L-Selectride	**b**: R_1=*n*Bu, R_2=H	78	>99:1
6	THF	DIBAL	MeMgBr	**c**: R_1=H, R_2=Me	82	93:7
7	Toluene	MeLi	L-Selectride	**d**: R_1=Me, R_2=H	77	94:6
8	THF	DIBAL	PhMgBr	**e**: R_1=H, R_2=Ph[d]	83	94:6
9	Toluene	PhLi	L-Selectride	**f**: R_1=Ph, R_2=H	25	60:40
10	Toluene	*n*BuLi	MeMgBr	**g**: R_1=*n*Bu, R_2=Me	60	>99:1
11	Toluene	MeLi	*n*BuMgCl	**h**: R_1=Me, R_2=*n*Bu	56	>99:1
12	Toluene	MeLi	PhMgBr	**i**: R_1=Me, R_2=Ph	68	>99:1
13	Toluene	PhLi	MeMgBr	**j**: R_1=Ph, R_2=Me	84	>99:1
14	Toluene	*n*BuLi	PhMgBr	**k**: R_1=*n*Bu, R_2=Ph	44	>99:1
15	Toluene	PhLi	*n*BuMgCl	**l**: R_1=Ph, R_2=*n*Bu	69	>99:1

[a] Isolated yield.

[b] The ratios **6**:**7** have been determined on the ^{1}H NMR spectra at 270 MHz of crude products by integration of the signals due to the bridgehead protons or the oxymethine protons.

[c] *n*Butyl.

[d] Phenyl.



Scheme 3. *Reagents and conditions*: (i) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt; (ii) ODCB, reflux.

Table 2. Studies of the oxidation of diol **6**

Entry	Substrate	Product **8**	Yield[a] (%)
1	**6a**	**8a**: R_1=H, R_2=^{n}Bu	66
2	**6b**	**8b**: R_1=^{n}Bu, R_2=H	61
3	**6c**	**8c**: R_1=H, R_2=Me	57
4	**6d**	**8d**: R_1=Me, R_2=H	45
5	**6e**	**8e**: R_1=H, R_2=Ph	65
6	**6f**	**8f**: R_1=Ph, R_2=H	48
7	**6g**	**8g**: R_1=^{n}Bu, R_2=Me	41
8	**6h**	**8h**: R_1=Me, R_2=^{n}Bu	45
9	**6i**	**8i**: R_1=Me, R_2=Ph	37
10	**6j**	**8j**: R_1=Ph, R_2=Me	40
11	**6k**	**8k**: R_1=^{n}Bu, R_2=Ph	42
12	**6l**	**8l**: R_1=Ph, R_2=^{n}Bu	45

[a] Isolated yield.

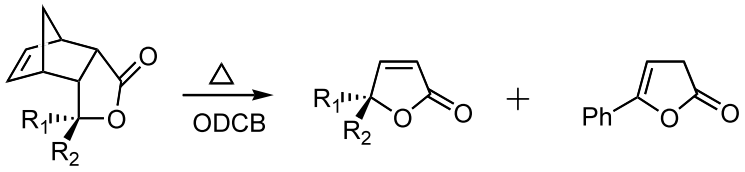
lower selectivity and yield were observed in the case of the phenyl group (entry 9). We next demonstrated similar construction of a quaternary asymmetric center (entries 10–15). In all cases, the reactions proceeded to furnish diol **6** diastereoselectively with 44–84% yield, and to construct quaternary asymmetric centers including alkyl and aryl moieties.[9] All of the diastereomeric diol **7** products were readily separated by silica gel column chromatography either directly or after conversion to lactone **8**. We believe that the diastereoselectivity in these reactions can be explained as follows. First, nucleophilic addition of R_1M to (−)-**1** gives the corresponding acetal derivative **4**, which is equilibrated to the metal-chelated intermediate **5**. Next, a second nucleophile (R_2M) approaches from the outside of the chelated ring to give a single stereoisomer. Thus, the newly generated asymmetric center is controlled selectively by the order in which the nucleophilic reagents are added (Scheme 2). We cannot, however, explain the lower selectivity in entry 9 (Table 1), though the reaction could possibly have proceeded through an acyclic intermediate.

As shown in Scheme 3 and Table 2, oxidation of diol **6** with a catalytic amount of tetrapropylammonium perruthenate (TPAP)[10] in the presence of 4-methylmorpholine *N*-oxide (NMO) gave the corresponding lactones **8**,[11] respectively, in 37–66% yield (Scheme 3, Table 2). Nuclear Overhauser effect (NOE) experiments were carried out for all of the lactones **8** because strong NOE was observed between the proton of the R_1 group and the olefinic proton in the bicyclo[2.2.1]heptene ring, and it was confirmed that the stereochemistry of the newly generated asymmetric centers, as shown in Scheme 3 and Table 2, was correct. A retro-Diels–Alder reaction of lactone **8** in refluxing *o*-dichlorobenzene (ODCB) yielded both enantiomers of corresponding γ-substituted butenolides **2** (Scheme 3, Table 3).[12] The absolute configurations of butenolides **2a**–**e** were assigned by comparison of their optical rotations with those reported previously.[13–17] Of these butenolides, compound **2b** is also known as β-angelica lactone, which is a key intermediate in the syntheses of some natural products such as (+)-blastmycinone,[18] (−)-saprathin,[19] and (+)-himbacine.[20] Because butenolide **2f** has never been reported,[21] the absolute configuration was deter-

Table 3. Studies of the retro-Diels–Alder reaction of lactone **8**

Entry	Substrate	Product **2**	Yield[a] (%)	$[\alpha]_D$[b] (*c*)	ee[c] (%)
1	**8a**	(+)-**2a**: R_1=H, R_2=^{n}Bu	84	+100.8 (1.0)	>98
2	**8b**	(−)-**2a**: R_1=^{n}Bu, R_2=H	85	−100.4 (1.2)[d]	>98
3	**8c**	(+)-**2b**: R_1=H, R_2=Me	61	+117.0 (1.3)[e]	>98
4	**8d**	(−)-**2b**: R_1=Me, R_2=H	52	−114.0 (0.8)[f]	>98
5	**8e**	(+)-**2c**: R_1=H, R_2=Ph	19	+277.2 (0.8)[g]	>98
6	**8f**	(−)-**2c**: R_1=Ph, R_2=H	12	−276.7 (0.7)	>98
7	**8g**	(−)-**2d**: R_1=^{n}Bu, R_2=Me	85	−19.1 (0.7)	>98
8	**8h**	(+)-**2d**: R_1=Me, R_2=^{n}Bu	77	+19.2 (1.2)[h]	>98
9	**8i**	(+)-**2e**: R_1=Me, R_2=Ph	92	+274.4 (1.2)[i]	>98
10	**8j**	(−)-**2e**: R_1=Ph, R_2=Me	83	−274.3 (1.3)[j]	>98
11	**8k**	(+)-**2f**: R_1=^{n}Bu, R_2=Ph	90	+163.1 (1.0)	>98
12	**8l**	(−)-**2f**: R_1=Ph, R_2=^{n}Bu	80	−161.4 (0.9)	>98

[a] Isolated yield.
[b] Measured in $CHCl_3$ at room temperature.
[c] Determined by HPLC with a chiral stationary phase (Chiralcel OD, eluent: 2-propanol-hexane).
[d] lit.[13a] −101.0.
[e] lit.[14e] +93.8 (*c* 0.5).
[f] lit.[14b] −107 (*c* 1.6).
[g] lit.[15b] +304 (*c* 1.0).
[h] lit.[16b] (29% ee) +4.6 (*c* 1.42).
[i] lit.[17b] +275.6 (*c* 1.0).
[j] lit.[17a] (91% ee) −248.3 (*c* 5.0).



8e: R_1 = H, R_2 = Ph (+)-**2c**: R_1 = H, R_2 = Ph **9**
8f: R_1 = Ph, R_2 = H (−)-**2c**: R_1 = Ph, R_2 = H

Scheme 4.

mined based on their connection with the structures of the starting diastereomeric lactones **8k** and **8l**. Entries 5 and 6 in Table 3 show that there was a lower yield in the retro-Diels–Alder reaction. In these cases, β,γ-unsaturated lactone **9** was also obtained in 8% yield with butenolide **2c** (Scheme 4). These results suggest the possibility of the racemization of **2** through a retro-Diels–Alder reaction. We therefore determined the enantiomeric excess (ee) of **2** by HPLC with a chiral stationary phase. Fortunately, all of the butenolides **2** existed in >98% ee. Thus, serious racemization had not occurred under these reaction conditions.[22]

In conclusion, we have established enantiodivergent syntheses of both enantiomers of several γ-substituted butenolides with tertiary and quarternary asymmetric centers from tricyclic lactone (−)-**1** as a single chiral material. This result means that these chiral butenolides can also be synthesized from enantiomeric lactone (+)-**1** by the same methods described above. Therefore, lactone **1** can be used enantiodivergently and enantioconvergently as a synthetic equivalent of both enantiomers of γ-substituted butenolides **2**. We have just begun to investigate exploitation of lactone **1** as a chiral butenolide equivalent for the synthesis of pharmacologically important natural and unnatural compounds.

Acknowledgements

We would like to thank Professor K. Ogasawara, Tohoku University, Sendai, Japan, and Dr. K. Kawamura, Nisshin Flour Milling Co. Ltd, Tokyo, Japan, for their many useful suggestions. We would also like to thank the Japan Association of Chemistry and Nisshin Flour Milling Co. LTD, Tokyo, Japan, for their financial support (to K.I.).

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22. In Ref. 4, we reported that ee values of (+)- and (−)-**2a** were 90–92% because of a partial racemizaton occurring under these reaction conditions. After the publication, we determined the ee of starting lactone **1**. Because the lactone **1** we used in Ref. 4 existed in 90% ee, no racemization occurred through the retro-Diels–Alder reaction. In this report, lactone **1** with >98% ee, which was synthesized by the method in Ref. 6, was used as a starting material.