Synthesis of optically active bicyclic lactone building blocks using catalytic enantioselective glyoxylate-ene reaction

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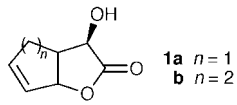
A new catalytic approach for the formation of optically active bicyclic lactones applying an enantioselective glyoxylate-ene reaction is presented; the catalytic reaction proceeds with formation of the two key stereogenic centers in good yield and with high diastereo- and enantio-selectivity.

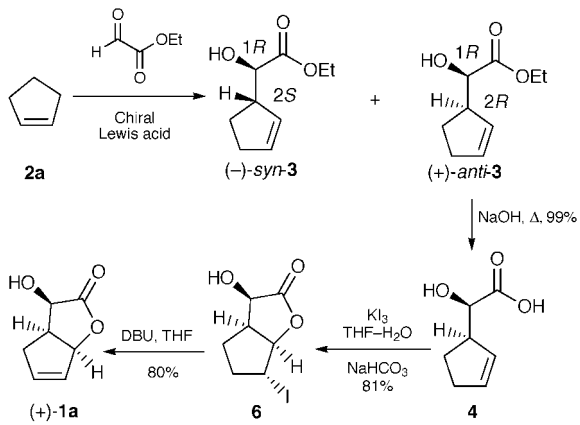
The bicyclic lactones **1** are key intermediates for the preparation of a wide range of natural products and biologically active compounds.[1] The lactone **1a** is a versatile building block for the synthesis of *e.g.* brefeldin A,[2a] carbovir,[2b] sesbanimide A and B,[2c] menovilin,[2d] aristeromycin,[2e] carbodine,[2e] carboxylic nucleosides[2f] and carbocyclic analogues of polytoxins and nikkomycines.[2g]



The synthesis of optically active **1a** has previously been accomplished by enzyme catalyzed kinetic resolution of the racemic compound prepared by the Diels–Alder reaction between glyoxylic acid and cyclopentadiene,[3] and more recently Helmchen *et al.* presented the preparation of **1a** using an asymmetric palladium-catalyzed allylic alkylation of 2-acetoxymalonates with cyclopent-2-enyl chloride.[4]

Here we present the first catalytic enantioselective ene reaction of cyclopentene **2a** with glyoxylate leading to a novel synthetic approach for the preparation of (+)-**1a** and by which the key stereogenic centres required for the synthesis of (+)-**1a** are formed in one step. The synthetic approach for (+)-**1a** is outlined in Scheme 1.

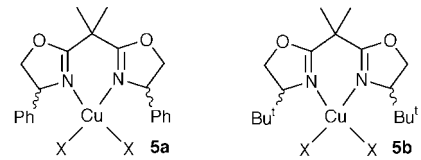
Recently, it has been shown that the bicyclic lactones **1b** can be prepared by a catalytic enantioselective hetero-Diels–Alder reaction of cyclohexadiene with glyoxylates catalyzed by C_2 bisoxazoline–copper(II) complexes followed by a rearrangement reaction.[5] Unfortunately, this methodology is not feasible for the reaction of cyclopentadiene with glyoxylates. However, the reaction of conjugated dienes with glyoxylates catalyzed by



Scheme 1

C_2 bisoxazoline–copper(II) complexes gives two products, the hetero-Diels–Alder and ene products,[5a] and recently Evans *et al.*[6] developed further the latter reaction for 1,1-disubstituted alkenes, hexene and cyclohexene with high yields and enantioselectivities.

The crucial step in the total synthesis of (+)-**1a** is the catalytic ene reaction of cyclopentene **2a** with ethyl glyoxylate. This reaction has been investigated in the presence of the C_2-symmetric bisoxazoline ligands **5a**,**b** and copper(II) salts as the



Lewis acids.† Some representative results are presented in Table 1.

The results in Table 1 show that the C_2 bisoxazoline–copper(II) complex catalyzed ene reaction of cyclopentene **2a** with ethyl glyoxylate proceed with excellent enantioselectivities for both diastereomers formed. The ligand (*S*)-**5b** gave the highest enantioinduction, with up to 98–99% ee (entries 3–5), while ligand (*R*)-**5a** gave the best diastereomeric *anti*-**3**:*syn*-**3** ratio (7.7:1) (entries 1, 6). Changing the enantiomer of the chiral ligand leads to the opposite enantiomer of *anti*-**3** (entries 1, 6), while changing the solvent to $MeNO_2$ leads to higher yield, however, a slight decrease in diastereo- and enantioselectivity (entry 7) is found. In an attempt to improve the enantioselectivity, the reaction was performed at lower temperature, but the conversion at 0 °C was very low (entry 5). An increase in the yield was achieved by increasing the catalyst loading to 25 mol%, without decreasing the diastereo- and enantio-selectivity of the products (entries 2, 6, 7). We have also investigated the enantioselective ene reactions catalyzed by (*R*)-**5a** and (*S*)-**5b** in other solvents and found that in Bu^tOMe, Et_2O and THF a lower yield of *anti*-**3** was isolated. A decrease in the diastereo- and enantio-selectivity was observed, except in Et_2O, where the *anti*-**3**:*syn*-**3** ratio was 5.1:1 with 91% ee and 89% ee

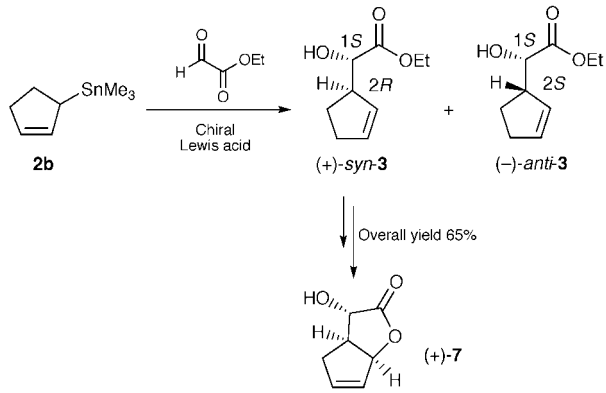
Table 1 Reaction of cyclopentene **2a** with ethyl glyoxylate in the presence of C_2-symmetric bisoxazoline–Cu^{II} salts (10 mol%) in CH_2Cl_2

					Ee (%)	
Entry	Catalyst	*T*/°C	Yield[a] (%)	*anti*-**3**:*syn*-**3**	*anti*-**3** (1*S*,2*S*)	*syn*-**3** (1*S*,2*R*)
1	(*R*)-**5a**–$Cu(OTf)_2$	25	38	7.7:1	91	89
2	(*R*)-**5a**–$Cu(OTf)_2$[b]	25	56	7.3:1	92	87
3	(*S*)-**5b**–$Cu(SbF_6)_2$[b]	25	66	2.2:1	98	97
4	(*S*)-**5b**–$Cu(SbF_6)_2$	25	55	2.8:1	98	96
5	(*S*)-**5b**–$Cu(SbF_6)_2$	0	~5	3.1:1	99	99
6	(*S*)-**5a**–$Cu(OTf)_2$[b]	25	54	7.7:1	92[c]	89[c]
7	(*S*)-**5a**–$Cu(OTf)_2$[bd]	25	72	3.9:1	83[c]	53[c]

[a] Isolated. [b] 25 mol% catalyst. [c] Opposite enantiomer compared with entry 2. [d] Solvent $MeNO_2$.

Table 2 Reaction of allyl stannane **2b** with ethyl glyoxylate in the presence of (*R*)-**5a**–$Cu(OTf)_2$ (10 mol%) in CH_2Cl_2

Entry	**2b** (equiv.)	Ethyl glyoxylate (equiv.)	*T*/°C	Yield (%)	*syn*-**3**: *anti*-**3**	Ee (%) *syn*-**3** (1*S*,2*R*)	Ee (%) *anti*-**3** (1*S*,2*S*)
1	1	2	25	98	2.2:1	24	54
2	1	10	25	99	2.4:1	43	81
3	1	10	−25	97	2.5:1	33	77
4	1	10	−78	99	2.7:1	35	69
5	2	1	25	98	2.3:1	22	24
6	2	1	−78	55	4.4:1	23	53



Scheme 2

for the two diastereomers, respectively. It should be noted that the absolute configuration of the ene-product *anti*-**3** is the same when using ligands (*R*)-**5a** and (*S*)-**5b** in combination with copper(II) as the Lewis acid (entries 2, 4). This phenomenon has been observed several times for these catalysts.[5,6]

From (+)-*anti*-**3** the desired bicyclic lactone (+)-**1a** can be obtained in a few steps (Scheme 1). Hydrolysis of the ester group was achieved using refluxing 3 M NaOH for 1 h giving **4** in quantitative yield. Iodolactonization of **4** using KI_3 and $NaHCO_3$ gave the iodide **6** in 81% yield. Elimination with DBU leads to (+)-**1a** in 80% yield.

By comparing the optical rotations of the bicyclic lactone **1a** to literature values[7] the absolute configuration was determined as (+)-**1a**, which leads to assignment of the absolute configuration as shown in Scheme 1.

We believed that an increase in the yield of the ene adduct could be obtained if a more active cyclopentenyl derivative was used. The allyl stannane **2b**[8] was therefore reacted with ethyl glyoxylate (Scheme 2), in the presence of C_2 bisoxazoline–copper(II) complexes; some results are presented in Table 2.

The allyl stannane **2b** was found to be more reactive than cyclopentene **2a** in the C_2 bisoxazoline–copper(II) catalyzed ene reaction with ethyl glyoxylate. At room temperature full conversion was observed in 5 min when using 2 equiv. of **2b** (entry 5). The yield for this reaction was very high, but the ee of the products was low (20% ee). When 1 equiv. of **2b** was used with 2 equiv. of ethyl glyoxylate the reaction was finished after 30 min (entry 1). The yield of the ene products *syn*-**3** and *anti*-**3** were also very good and the ee of the minor product increased to 54% ee. However the ee of the major diastereomer *syn*-**3** remained below 25% ee. By using a larger excess of ethyl glyoxylate at room temperature the ee of the major diastereomer was increased to 43% ee, with 81% ee for the minor diastereomer (entry 2). When the reaction was performed at lower temperatures (−25 and −78 °C) no improvement in the ee of the products was observed (entries 3,4). When using 1 equiv. of ethyl glyoxylate the yield was found to decrease from 98% at room temperature to 55% at −78 °C (entries 5,6). The reason for this drop in yield is attributed to the ethyl glyoxylate oligermerizing due to the extended reaction time. The ee of the major product is not dependant on the temperature of the reaction, whereas an increase from 24 to 53% ee was observed for the minor diastereomer by decreasing the temperature to −78 °C. The diastereoselectivity was also improved from 2.3:1 to 4.4:1 by reducing the temperature (entries 5,6).

The formation of (+)-*syn*-**3** in the catalytic enantioselective ene reaction using the allyl stannane **2b** as the substrate leads to a simple synthetic procedure for the formation of the other diastereomer, (+)-**7**, of (+)-**1a** in 65% overall yield as presented in Scheme 2.

In conclusion we have presented the development of highly diastereo- and enantio-selective ene reactions of cyclopentenes with ethyl glyoxylate leading to the formation of products, which in a few steps give highly attractive optically active bicyclic lactones. Work is in progress to develop this approach further.

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Notes and references

† *General procedure* for the catalytic ene reaction: A flame dried Schlenk tube was charged with ligand (*S*)-**5a** (84 mg, 0.25 mmol) and $Cu(OTf)_2$ (90 mg, 0.25 mmol) and stirred vigorously *in vacuo* for 1.5 h. Dry CH_2Cl_2 (3 ml) was added and the green suspension stirred until a clear solution formed (2 h). Freshly distilled ethyl glyoxylate (1.02 g, 10 mmol) in toluene (0.25 ml) was added at room temperature followed by the addition of cyclopentene **2a** (88 μl, 1.0 mmol) and stirred for 48 h. The reaction solution was purified by flash chromatography (25% Et_2O–hexane) to give *anti*-**3** in 48% yield (82 mg, 0.48 mmol). A small amount of the lower R_f diastereomer *syn*-**3** was isolated in 6% yield (10 mg, 0.06 mmol). *Selected data* for (+)-*anti*-**3**: $[\alpha]_D^{20}$ +1.25 (*c* 2.5, $CHCl_3$); $\delta_H(CDCl_3)$ 5.94 (ddd, *J* 5.5, 4.4, 2.2, 1H), 5.50 (ddd, *J* 6.1, 4.4, 2.2, 1H), 4.30–4.19 (m, 2H), 4.11 (dd, *J* 7.5, 4.5, 1H), 3.16–3.00 (m, 1H), 2.51 (d, *J* 7.5, 1H), 2.40–2.18 (m, 2H), 2.10–1.98 (m, 1H), 1.92–1.80 (m, 1H), 1.30 (t, *J* 7.2, 3H). $\delta_C(CDCl_3)$ 174.37, 135.02, 128.16, 73.11, 61.42, 49.89, 32.48, 25.85, 14.23; ν_{max}(film)/cm^{-1} 3496, 2941, 2852, 1732, 1446, 1368, 1259, 1197, 1159, 1097, 1027. (HRMS: calc. 170.0943, found 170.0945); *m*/*z* (EI) 170 (M^+), 152, 133, 123, 104, 97, 79, 76, 67 (100%); GC (Chiralsil-DEX CB, *T*. 100 °C, flow rate = 2 ml min^{-1}, retention time = 10.74 min (major, 1*R*,2*R*), 11.90 min (minor, 1*S*,2*S*). For (−)-*syn*-**3**: $[\alpha]_D^{20}$ −0.48 (*c* 3.5, $CHCl_3$); $\delta_H(CDCl_3)$ 5.89 (ddd, *J* 5.5, 4.4, 2.2, 1H), 5.66 (ddd, *J* 6.1, 4.4, 2.2, 1H), 4.31–4.20 (m, 3H), 3.20–3.10 (m, 1H), 2.75 (br s, 1H), 2.48–2.24 (m, 2H), 1.95–1.67 (m, 2H), 1.30 (t, *J* 7.1, 3H); $\delta_C(CDCl_3)$ 174.49, 133.66, 130.19, 72.37, 61.65, 49.94, 32.35, 23.41, 14.26; ν_{max}(film)/cm^{-1} 3495, 2962, 1733, 1457, 1368, 1260, 1195, 1157, 1096, 1021 (HRMS: calc. 170.0943, found 170.0944); *m*/*z* (EI) 170 (M^+), 152, 133, 123, 104, 97, 79, 76, 67 (100%). GC (Chiralsil-DEX CB, *T* 100 °C, flow rate = 2 ml min^{-1}, retention time = 12.55 min (major, 1*R*,2*S*), 13.70 min (minor, 1*S*,2*R*).

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