Enantioselective Syntheses of (−)- and (+)-Homocitric Acid Lactones

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Highly enantioselective syntheses of enantiomers of homocitric acid lactones (*R*)-**5a** and (S)-**5b** are described. Thermal Diels−Alder cycloadditions of **2a** and **2b** to 1,3-butadiene produced adducts **3a** and **3b**, respectively. Oxidative ozonolysis of latter adducts gave products **4a** and **4b** which after acid treatment afforded a mixture with **5a** and **5b** as major component. Acid lactones **5a** and **5b** were converted into their dimethyl esters **6a** and **6b** which were purified by chromatography. After saponification, the products obtained were crystallized to yield (−)- and (+)-homocitric acid lactones ((*R*)-**5a** and (*S*)-**5b**). Diastereomeric excess (de) of Diels−Alder adducts **3a** and **3b** was determined by means of Mosher esters of glycols **8a**, **8b**, and racemic **8**. Diels−Alder cycloaddition products of lactones **2a** and **2b** to 1,3-butadiene showed a diastereoselectivity of 96%.

(−)-Homocitric acid (**1a**), an intermediate in the biosynthetic pathway of lysine in yeast and some fungi, is produced by enzymatic condensation of α-ketoglutarate and acetylSCoA (Figure 1).[1]

Two syntheses of the homocitric acid lactone **5** have been described: as a racemate, by hydrolysis of the cyanohydrin of diethyl *β*-ketoadipate and as the (*S*)-enantiomer by degradation of (−)-quinic acid of known absolute configuration in order to determine the absolute configuration of the natural product.[2,3] However, no enantioselective synthesis of the natural enantiomer of homocitric acid **1a** has ever been reported.

In the present paper we describe enantioselective syntheses of (−)-(*R*)- and (+)-(*S*)-homocitric acid lactones (**5a** and **5b**) from (−)-L-lactic acid and (−)-L-serine, respectively. The key step in the synthetic pathway is the highly diastereoselective Diels−Alder reaction of dienophiles **2a** and **2b** with 1,3-butadiene.

A possible retrosynthetic analysis of the (−)-homocitric acid ((*R*)-**1**) is as shown (Scheme 1). The enantioselective step **A** → **B** relies on a highly diastereoselective Diels−Alder reaction of dienophile **2** with 1,3-butadiene.

Dienophile **2** was selected as a synthetic equivalent of synthon **B** because there is in its structure an acetal moiety which acts not only as a chiral auxiliary in the Diels−Alder reaction but also as a protecting group in the subsequent degradation. This synthetic equivalent has already been described in its enantiomeric forms: **2a** synthesized from (−)-L-lactic acid with an enantiomeric excess (ee) of 96% and **2b** from (−)-L-serine with an ee of 99% (Scheme 2).[4,5]

Heating of 1,3-butadiene and dienophile **2** at 120 °C gave the Diels−Alder product **3** isolated as an oil in a yield of 51%.[6,7] For the determination of the degree of diastereoselectivity, the adduct **3** was converted to its Mosher ester (**8**) by reduction to diol **7** with lithium aluminum hydride followed by esterification with (+)-methoxy(trifluoromethyl)phenylacetyl chloride ((+)MTPACl) (Scheme 3).[8] In order to distinguish the methoxyl and trifluoromethyl resonances in the ^1H and ^{19}F NMR spectra of the MTPA ester **8** produced from racemic adduct **3**, it was necessary to add Eu(fod)$_3$.[9,10] The ester prepared from **3a** was submitted to the same procedure, and the ee was determined to be 92%; the diastereose-

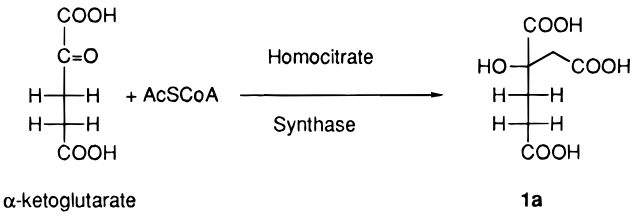
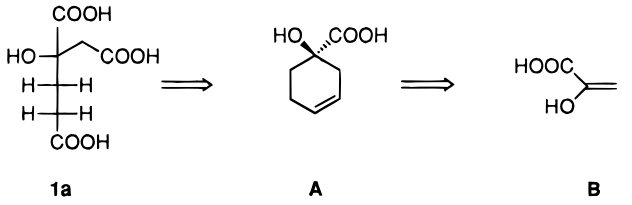
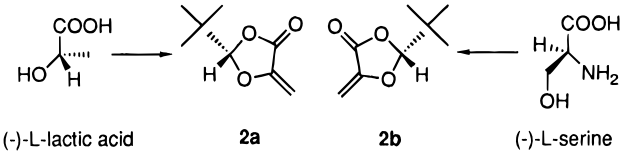


Figure 1.

Scheme 1



Scheme 2



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(6) The other 49% consisted of gummy polymeric products of **2** and 1,3-butadiene. Dienophile **2** proved to be an unstable compound: it readily polymerized when left at rt for several hours.

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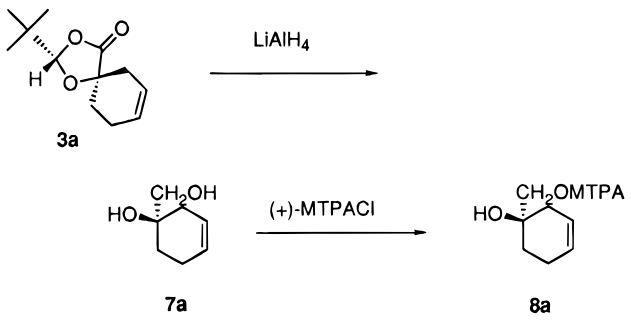
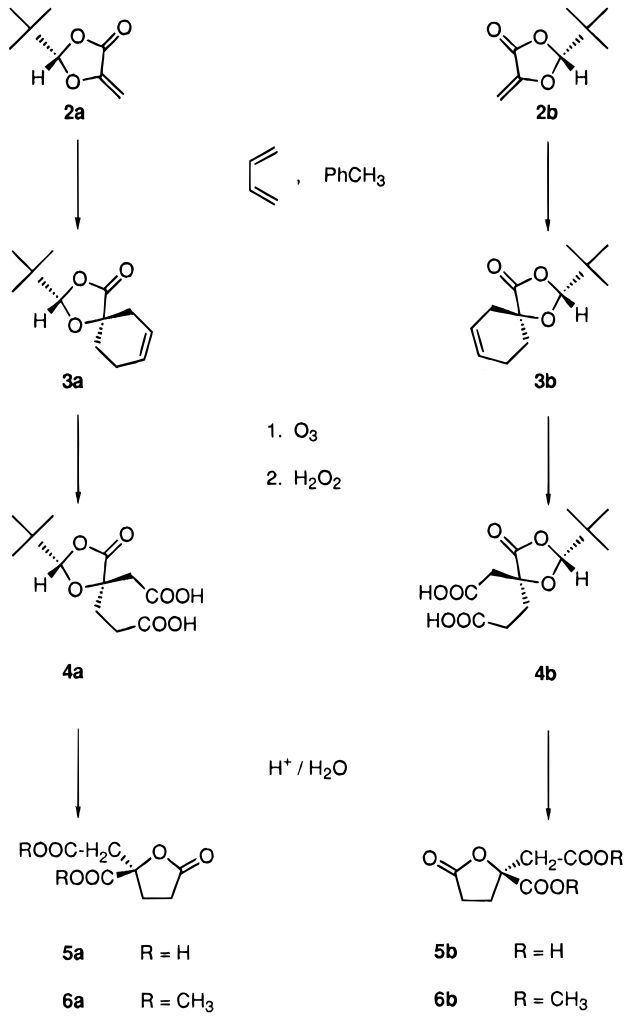
Scheme 3



Scheme 4



lectivity of the Diels−Alder reaction of dienophile **2a** with 1,3-butadiene was 96%.

Ozonolysis of the double bond in adduct **3a** followed by oxidative workup afforded **4a** as an oil in a 90% yield.[11] Deprotection of diacid **4a** with aqueous formic acid gave (−)-homocitric acid (**1a**) which immediately cyclized to the γ-lactone **5a** (Scheme 4). However, all attemps to crystallize the latter compound failed. Lactone **5a** was converted into its dimethyl ester by (trimethylsilyl)-diazomethane and purified by column chromatography.[12]

Saponification of the diester **6a** yielded (−)-homocitric acid lactone (**5a**), whose properties were in good agreement with those reported for the natural product isolated from *Sacharomyces cerevisiae*.[1,13]

The enantioselective synthesis of (+)-homocitric acid lactone (**5b**) was straightforward; it started with dienophile **2b** (ee = 99%) prepared from (−)-L-serine. As described for **2a**, lactone **2b** was subjected to Diels−Alder reaction with 1,3-butadiene. Isolated adduct **3b** showed an optical rotation of $[\alpha]_D = -17.5°$ (c = 1.2, $CHCl_3$), which compared well to the rotation of its enantiomer **3a** $[\alpha]_D = +16.3°$ (c = 1.0, $CHCl_3$) described above. The diastereoselectivity of the thermal Diels−Alder cycloaddition of 1,3-butadiene with lactone **3b** as determinated from its Mosher ester **8b** was 96%. Adduct **3b** was converted to the homocitric acid lactone **5b** as described above.[14]

The key step in the synthetic pathway is the formation of the asymmetric center of the target molecule by means of a highly stereoselective thermal Diels−Alder reaction. This high selectivity is achieved thanks to the bulkiness of the *tert*-butyl group in the acetal portion of the dienophile, which directs the attack of the 1,3-butadiene molecule to the opposite side of the molecule.[15] There exists in the literature only a few cases of asymmetric thermal Diels−Alder reactions with such a high degree of stereoselectivity; our adduct formation belongs to this small group.[4c,7] On the other hand acidic hydrolysis of **6a** was avoided due to poor results obtained with **4a**. Then saponification with a NaOH solution was tried, and this proved to work well: both esters were hydrolyzed and the chiral center remained untouched (no racemization was detected), meaning that the reaction proceeded via an alkyl cleavage mechanism.

In conclusion, highly enantioselective syntheses of (+)- and (−)-homocitric acid lactones ((*R*)-**5a** and (*S*)-**5b**) from (−)-L-lactic acid and (−)-L-serine, respectively, have been achieved (96% ee). The key step of the synthetic route is a highly stereoselective thermal Diels−Alder reaction of dienophile **2** with 1,3-butadiene (96%). These results should induce studies on (−)-homocitric acid lactone biosynthesis, namely, the enzymes involved in its biosynthetic pathway which could be targets of inhibitors to avoid the development of certain fungi.

Experimental Section

General. NMR spectra were obtained on 200 or 400 MHz spectrometers, and all ^1H NMR spectra were referenced to TMS as internal standard. $[\alpha]_D$ values were determined at 20 °C. IR data are expressed in units of frequency (cm^{-1}). Low-resolution mass spectra were measured at 70 eV. Elemental analyses were performed by Service de Microanalyse de la Faculté de Chimie de l'Université Louis Pasteur. Melting points (mp) are not corrected.

Toluene, methanol, ether, and pyridine were distilled from CaH_2 under Ar just before use. Merck silica gel 60 (0.062−0.200 mm) was used for column chromatography.

(2*S*,5*R*)-1,3-Dioxaspiro[4,5]-2-*tert*-butyldec-7-en-4-one (3a). A solution of dienophile **2a** (9.3 g, 60 mmol), toluene

(10) The MTPA ester **8** from racemic adduct **3** did not show any distinction of the signals produced by diastereoisomeric methoxy and trifluoromethyl groups in ^1H and ^{19}F NMR; however, in presence of Eu(fod)$_3$ in a 0.3 molar ratio to the Mosher ester both signals were split, see ref 9.

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(13) Our sample, mp 146−148 °C; $[\alpha]_D$ −51° (c = 0.19, see ref 17); natural product, mp 145−146 °C; $[\alpha]_D$ −52.6° (c = 0.19, see ref 17).

(14) The (+)-homocitric acid lactone (*S*)-**5** showed mp 144−147 °C and $[\alpha]_D$ +54 (c = 0.21, see ref 17). These values are in accordance with the ones obtained from the resolution of the racemic compound with brucine in ref 2.

(15) In **2a** the attack of 1,3-butadiene is mainly on the Re face of the molecule and in **2b** is mainly on the Si face.

(2 mL), hydroquinone (200 mg), and 1,3-butadiene (2000 mol %) in a sealed glass vial was heated at 120 °C for 48 h. The reaction mixture was flash distilled to eliminate toluene and 1,3-butadiene, and then a bulb-to-bulb distillation (140 °C/2 mmHg) afforded 6.4 g (51%) of **3a**: $[\alpha]_D = +16.3°$ ($c = 1.01$, $CHCl_3$); IR ($CHCl_3$) 3030, 2960; ^1H NMR ($CDCl_3$) 5.8, 5.6, 5.2, 2.3, 1.9, 0.96; MS *m*/*z* 210 (M^+). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.49; H, 8.68.

(2*R*,5*S*)-1,3-Dioxaspiro[4,5]-2-*tert*-butyldec-7-en-4-one (3b). The same procedure as for lactone **3a** starting from dienophile **2b** was used. Data for lactone **3b**: $[\alpha]_D = -17.2°$ ($c = 1.18$, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.61.

(2*S*,5*R*)-2-*tert*-Butyl-5β-(carboxyethyl)-5-(carboxymethyl)-1,3-dioxolan-4-one (4a). A solution of the Diels−Alder adduct **3a** (500 mg, 2.38 mmol) in MeOH (20 mL) was ozonized at −78 °C until the solution turned to a light blue; excess ozone was removed with Ar (15 min). The reaction mixture was left to reach rt, and the solvent was evaporated. The residue was treated with a solution of 90% HCOOH (4 mL) and 30% H_2O_2 (4 mL) and stirred overnight. After evaporation, 600 mg (90%) of the diacid **4a** was obtained as an oil: $[\alpha]_D = -21.1°$ ($c = 1.10$, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.3, 2.9, 2.8, 2.55, 2.18, 0.97.

(2*R*,5*S*)-2-*tert*-Butyl-5β-(carboxyethyl)-5-(carboxymethyl)-1,3-dioxolan-4-one (4b). The same procedure as above was used. Data for diacid **4b**: $[\alpha]_D = +20.5°$ ($c = 1.07$, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.3, 2.9, 2.8, 2.55, 2.18, 0.97.

Dimethyl Ester of (−)-Homocitric Acid Lactone (6a). A solution of **4a** (400 mg, 1.45 mmol) in 80% HCOOH (25 mL) was heated under reflux for 2 h, cooled, and concentrated.[16] Part of the crude product obtained (200 mg) was disolved in methanol (3 mL) and ether (6 mL); then a 2 M solution of $(CH_3)_3SiCHN_2$ in hexane was added dropwise until the reaction mixture turned a light yellow. After 1 h of stirring, 90% HCOOH was added to eliminate excess $(CH_3)_3SiCHN_2$. The solvent was removed, and chromatography on silica gel (hexane/AcOEt 50%/50%) afforded 112 mg (48%) of **6a** as an oil: $[\alpha]_D = -10.6°$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$) 1788, 1737, 1226; ^1H NMR ($CDCl_3$) 3.76, 3.65, 3.19, 3.03, 2.5; MS *m*/*z* 216 (M^+). Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.55. Found: C, 50.16; H, 5.38.

Dimethyl Ester of (+)-Homocitric Acid Lactone (6b). The same procedure as above was used. Data for lactone **6b**: $[\alpha]_D = +11.7°$ ($c = 0.95$, $CHCl_3$). Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.55. Found: C, 50.12; H, 5.41.

(−)-Homocitric Acid Lactone (5a). The dimethyl ester of (−)-homocitric acid lactone (**6a**) (100 mg, 0.4 mmol) was added to 0.2 N sodium hydroxide (15 mL), and the resulting mixture was refluxed for 6 h. The reaction was cooled to rt, and 1 N HCl was added until a pH = 1 was obtained. Then the mixture was evaporated, dissolved in acetone, filtered, and again evaporated. The solid obtained was dissolved in hot AcOEt, filtered, evaporated, and recrystallized from AcOEt−hexane to yield 30 mg (34%) of the (−)-homocitric acid lactone (**5a**) mp 146−148 °C; $[\alpha]_D = -51°$ ($c = 0.19$, conditions as in ref 17); IR (KBr) 1765, 1722, 1672, 1184; ^1H NMR ($(CD_3)_2CO$) 3.17, 3.03, 2.5; ^{13}C NMR ($(CD_3)_2CO$) 176.5, 172.5, 170.5, 83.5, 41.7, 31.9, 28.3. Anal. Calcd for $C_7H_8O_6$: C, 44.68; H, 4.25. Found: C, 44.71; H, 4.58.

(+)-Homocitric Acid Lactone (5b). The same procedure as above was used. Data for **5b**: mp 144−147 °C; $[\alpha]_D = +54°$ ($c = 0.21$, conditions as in ref 17). Anal. Calcd for $C_7H_8O_6$: C, 44.68; H, 4.25. Found: C, 44.95; H, 4.28.

Diastereoisomeric Excess Determination of the Diels−Alder Adducts. 1. 1-Hydroxycyclohex-3-enemethanol (7a). To a suspension of $LiAlH_4$ (200 mg) in ether (5 mL) was added a solution of the adduct **3a** (100 mg, 0.47 mmol) in ether (10 mL). After 18 h of stirring at 20 °C, a saturated solution of Na_2SO_4 was added, the obtained suspension was filtered, and the organic layer was dried with $MgSO_4$ and evaporated to yield 50 mg (78%) of the glycol **7a** as an oil: $[\alpha]_D = +16.5°$ ($c = 0.36$, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.6, 3.51, 2.12, 1.68.

2. 1-Hydroxycyclohex-3-enemethanol (7b). The same procedure as above was used. Data for **7b**: $[\alpha]_D = -17.2°$ ($c = 0.32$, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.6, 3.51, 2.12, 1.68.

3. (+)-MTPA Esters (8). A solution of pyridine (300 μL), (+)-MTPA-Cl (50 μL), glycol **7a** or its enantiomer **7b** (20 mg, 0.148 mmol), and CCl_4 (300 μL) was stirred under Ar overnight at rt. Then (dimethylamino)propylamine (50 μL) was added, and after 15 min the solution was diluted with ether and washed subsequently with diluted HCl, saturated Na_2CO_3, and brine. The organic layer was dried with $MgSO_4$ and evaporated. Then CCl_4 was added and evaporated. This was repeated twice. Finally Eu(fod)$_3$ (48 mg, 0.0468 mmol) was added, and the mixture was dissolved in $CDCl_3$. The sample for NMR studies was taken from this solution: ^1H NMR ($CDCl_3$) 4.6; ^{19}F NMR ($CDCl_3$) −70.83.

The racemic Diels−Alder adduct **3** (prepared from racemic lactic acid and using the same synthetic pathway as for **3a**) was subjected to reduction, and the racemic glycol was esterified with (+)-MTPA-Cl and analyzed as previously described. The obtained NMR results were as follows: ^1H NMR ($CDCl_3$) 4.9, 4.85, 1:1 ratio; ^{19}F NMR ($CDCl_3$) −70.85, −70.87, 1:1 ratio.

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(16) This afforded a mixture of compounds which showed in NMR analysis the (−)-(*R*)-homocitric acid lactone **5a** as the major component.

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