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TETRAHEDRON: *ASYMMETRY*

Improved synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid

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Abstract

A facile synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxylic acid on a multigram scale, that starts from inexpensive, commercially available compounds, is described.

1. Introduction

trans-Cyclohex-4-ene-1,2-dicarboxylic acids **4** and *ent*-**4** are versatile chiral building blocks which have found numerous applications in the synthesis of complex molecular architectures, including natural products.[1–5] Recently we have introduced a novel application of this synthon, by demonstrating that the *cis* diol obtained by osmium dihydroxylation of **4** can be effectively used as a 3,4-disubstituted galactose mimic in the synthesis of pseudo-oligo saccharides.[6] We now report a facile enantioselective preparation of both enantiomers of **4**, which can be carried out on a multigram scale with high-yields, starting from inexpensive reagents and without intermediate purifications.

Besides classical resolution procedures,[2] various syntheses have been reported for the title compound, and are summarized below.

(i) Syntheses based on Diels–Alder reactions of chiral fumarates. The reaction was pioneered by Walborsky[1,2] and improved by H. Yamamoto[3] using dimenthyl fumarate. These reactions are reported to occur with very high yields and diastereoisomeric excess[4] and have been used for the synthesis of cyclohex-4-ene-1,2-dihydroxymethylene in enantiomerically pure form. However, they are not useful for the stereoselective synthesis of the diacid, since the dimenthyl ester extensively epimerizes and racemizes upon basic hydrolysis or under transesterification conditions.[5] Alternatively, the diacid can be synthesized following Helmchen's procedure,[7] starting from the

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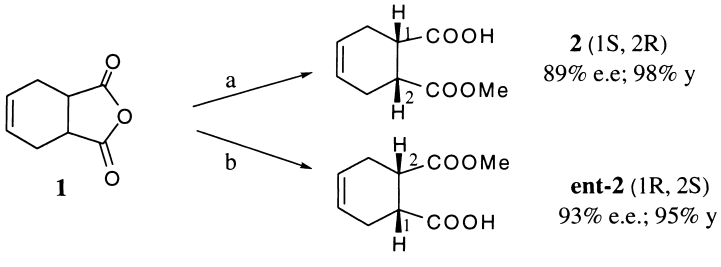
diethyl-lactylfumarate and using Ti catalysts. The resulting diester can be hydrolyzed with no loss of configurational integrity using LiOH in MeOH/H_2O.[8] However, butadiene is not the best substrate for Helmchen's reaction and, on multigram scale, only diastereomeric ratios of up to 6:1 were obtained.[8]

(ii) Syntheses based on Diels–Alder reactions using chiral catalysts. Although many catalysts have been discovered for the enantioselective Diels–Alder reaction, few of them have been reported to be effective for fumarate cycloadditions[9–12] and, to the best of our knowledge, only one has been described to promote the cycloaddition of butadiene to diethyl fumarate with 60% e.e.[9]

(iii) Synthesis based on enzymatic desymmetrization of the *cis* diester. Desymmetrization of the *meso* dimethyl *cis*-cyclohex-4-ene-1,2-dicarboxylate using pig liver esterase (PLE) proceeds with high yields to give the (+)-(1*R*,2*S*) enantiomer of the monoacid in >94% e.e.[13] Treatment of this compound with *t*BuOK results in the regioselective epimerization of C2 and affords the *trans*-(1*R*,2*R*) monoacid as a 4:1 mixture with the starting *cis*-stereoisomer.[14] Separation of these compounds is exceedingly difficult, and can only be achieved by gradient column chromatography followed by fractional distillation.[14] The (1*S*,2*S*) enantiomer cannot be synthesized directly from this route.†

2. Results and discussion

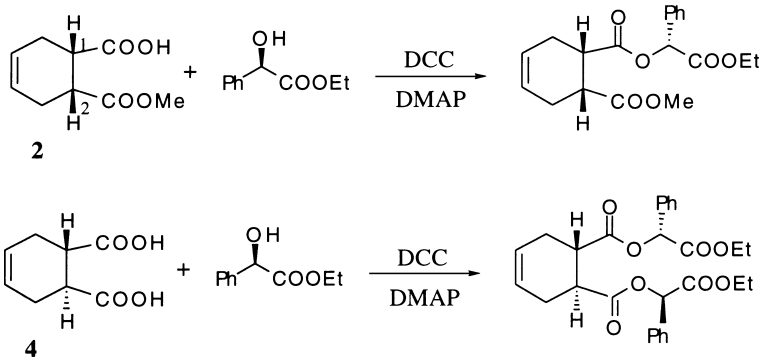
We now present an improved synthesis of both enantiomers of the title compound, that takes advantage of the chemical desymmetrization of anhydrides recently introduced by Bolm (Scheme 1).[15] Treatment of the commercially available tetrahydrophthalic anhydride **1** with MeOH at −50°C in the presence of 1.1 mol/equiv. of quinine or its quasienantiomer quinidine results in the highly stereoselective formation of the (1*S*,2*R*) monoacid **2** (e.e. 90%) or the (1*R*,2*S*) enantiomer *ent*-**2** (e.e. 93%), respectively. After extraction of the base with HCl, the crude acids could be used without further purification. (The chiral base could be quantitatively recovered by precipitation with 3 M NaOH.) The reaction could be carried out on multigram scale with almost quantitative yield and consistently high stereoselectivity. The e.e.s were determined by determining the specific rotations of the monoacids **2** and *ent*-**2** and confirmed by ^{1}H NMR of the corresponding ethylmandelate esters in C_6D_6[16] (Scheme 2).



a. MeOH, quinine. b. MeOH, quinidine.

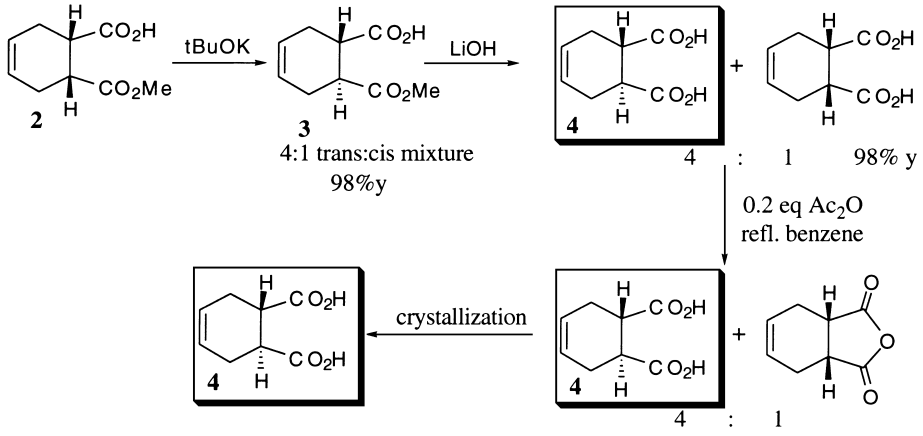
Scheme 1. Bolm's desymmetrization of tetrahydrophthalic anhydride

† This compound can be prepared starting from the (+)-(1*R*,2*S*) enantiomer of the monoacid by orthogonal protection of the acid (e.g. as a *t*Bu ester), followed by hydrolysis of the methylester at C2, and C1 epimerization with *t*BuOK: unpublished results from this laboratory.



Scheme 2. Synthesis of the ethyl mandelates

Starting from **2**, the (1*S*,2*S*)-*trans* diacid **4** was obtained by the sequence depicted in Scheme 3. Thus, *t*BuOK epimerization gave the 4:1 *trans*:*cis* mixture described by Seebach.[14‡] Separation was not attempted at this stage, but the crude was hydrolyzed (LiOH, MeOH) to give the desired diacid **4**, contaminated by 20% of the *cis* isomer. The latter was selectively transformed in the starting tetrahydrophthalic anhydride **1** by treating the crude hydrolysis product with 0.2 mol/equiv. of Ac_2O in refluxing benzene for 2 h. Under these conditions the *trans* diacid **4** was left unchanged and could be isolated in 80% yield from the reaction crude by crystallization from benzene. A second crop of almost pure *trans* diacid may be recovered by dissolving the mother liquor in dry dichloroethane and reacting the anhydride with 1 mol/equiv. of polyethyleneglycol of MW 4600 for 18 h at reflux. This allows recovery of the remaining diacid **4** after Et_2O precipitation of the acylated polyethyleneglycol. Trapping of the anhydride could also be achieved by using 1.1 equiv. of Wang resin in refluxing dichloroethane.



Scheme 3. Stereoselective synthesis of (1*S*,2*S*)-*trans*-cyclohex-4-ene-1,2-dicarboxylic acid **4**

The enantiomeric excess of the diacid was checked at this stage both by determining the specific rotation and by synthesizing the bis-mandelate ester (Scheme 2),[16] and it was found to be 86%.

The whole sequence does not require any intermediate purification, and can be run on a multigram scale in a matter of days, with >60% total yield starting from the tetrahydrophthalic anhydride.

‡ The reaction must be carried out in THF at room temperature for 1 h. If the reaction conditions are forced (longer time, higher concentration or temperature), some transesterification also takes place, yielding variable amounts of a mono *t*-butylester, which can be hydrolyzed to the diacid by treatment of the crude with trifluoroacetic acid in quantitative yield.

The same sequence can be run starting from the (1*R*,2*S*) enantiomer *ent*-**2** of 93% e.e. to give the (1*R*,2*R*)-*trans*-cyclohex-4-ene-1,2-dicarboxylic acid *ent*-**4** with 88% e.e.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra were recorded at 50 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane; coupling constants are reported in hertz. All solvents were dried before use: THF using Na/benzophenone; benzene and toluene using Na; CCl_4 using 4 Å molecular sieves; CH_2Cl_2 using CaH_2.

3.2. Synthesis of (1S,2R)-cyclohex-4-ene-1,2-carboxylic acid monomethylester **2**

To a suspension of tetrahydrophthalic anhydride **1** (5 g, 32.9 mmol, 1 equiv.) and quinine (11.8 g, 36.4 mmol, 1.1 equiv.) in 1:1 toluene:CCl_4 (150 ml) MeOH (4 ml, 98.7 mmol, 3 eq) was added dropwise, under N_2 at −50°C. The solution was stirred at this temperature for 24 h, then the solvent was evaporated, the residue dissolved in AcOEt, and the organic phase extracted with 6N HCl. The organic solvent was dried with Na_2SO_4 and evaporated to yield 5.9 g of the *cis* monomethylester **2** (98%), which was used without further purification. $[\alpha]_D$ −13.7 (*c* 1.52, EtOH) {lit.[14] for the (1*R*,2*S*) enantiomer $[\alpha]_D$ +14.9 (*c* 1.48, EtOH)}. ^{1}H NMR (200 MHz, $CDCl_3$): 2.3–2.7 (m, 4H), 3.1 (m, 2H, H_1 and H_2), 3.7 (s, 3H, COO*Me*), 5.7 (m, 2H, H_4 and H_5). ^{13}C NMR (50 MHz, $CDCl_3$): 25.4, 25.6, 39.3, 39.5, 51.8, 124.9, 125.0, 173.6, 179.6. The e.e. of **2** was determined to be 89% by synthesizing the mandelate ester (Scheme 2) according to the reported procedure.[16] ^{1}H NMR (C_6D_6, 200 MHz): 0.8 (t, 3H, J=7 Hz); 2.0–2.3 (m, 1H); 2.65–2.90 (m, 4H); 3.0–3.1 (m, 1H); 3.32 (s, 3H); 3.70–3.95 (m, 2H); 5.5 (m, 1H); 6.08 (s, 1H).

3.3. Synthesis of (1R,2S)-cyclohex-4-ene-1,2-carboxylic acid monomethyl ester ent-**2**

The same procedure as above was used; but quinidine (11.8 g, 36.4 mmol, 1.1 equiv.) was used instead of quinine.

The crude (1*R*,2*S*) monomethyl ester had $[\alpha]_D$ +13.7 (*c* 1.59, EtOH) {lit.[14] $[\alpha]_D$ +14.9 (*c* 1.48, EtOH)}. The e.e. of *ent*-**2** was determined to be 93% by synthesizing the mandelate ester (Scheme 2) according to the reported procedure.[16] ^{1}H NMR (C_6D_6, 200 MHz): 0.8 (t, 3H, J=7 Hz); 2.0–2.3 (m, 1H); 2.5–2.9 (m, 4H); 3.0–3.1 (m, 1H); 3.30 (s, 3H); 3.70–3.95 (m, 2H); 5.5 (m, 1H); 6.12 (s, 1H).

3.4. cis–trans Equilibration of the monomethyl ester. Synthesis of **3**

To a stirred solution of *t*BuOK (5.24 g, 46.7 mmol, 1.5 equiv.) in dry THF (27 ml), a solution of **2** (5.73 g, 31.1 mmol, 1 equiv.) in THF (67 ml) was added under N_2 at 0°C. The solution was stirred at room temperature for 1 h, then concentrated under vacuum to about 1/3 of the original volume and 6N HCl was added to pH=1. The aqueous phase was extracted with Et_2O, the organic phases dried with Na_2SO_4 and the solvent evaporated, to yield 5.67 g of crude in a 4:1 **3**:**2** mixture, as evaluated by ^{1}H NMR. ^{1}H NMR (200 MHz, $CDCl_3$): 2.1–2.7 (m), 2.9 (m, 2H, H_1 and H_2 of the *trans* isomer **3**), 3.1 (m, 2H, H_1 and H_2 of the *cis* isomer **2**), 3.7 (s), 5.7 (m).

3.5. Methylester hydrolysis. Synthesis of **4**

To a solution of a 4:1 mixture of the *trans* and *cis* monomethyl esters **3** and **2** (1 g, 5.4 mmol, 1 equiv.) in 3:1 MeOH:H_2O (8 ml) LiOH·H_2O (863 mg, 20.6 mmol, 3.8 equiv.) was added. The solution was stirred at room temperature for 2 h, then concentrated under vacuum before adding 6N HCl to pH=1. The aqueous phase was extracted with AcOEt, the organic solvent dried with Na_2SO_4 and evaporated to yield 870 mg of 4:1 *trans:cis* diacids (95%). ^{1}H NMR (200 MHz, $CDCl_3$): 2.1–2.7 (m); 2.0 (m, 1H of the *trans* diacid); 3.0–3.2 (2m, 1H of the *cis* diacid); 5.7 (m).

3.6. Isolation of **4**

To a solution of a 4:1 mixture of the *trans* and *cis* diacids (933 mg total, containing 186.6 mg of *cis* diacid, 1.09 mmol, 1 equiv.) in dry benzene (10 ml) Ac_2O (120 μl, 1.09 mmol, 1 equiv.) was added under N_2. The solution was warmed to reflux for ca. 2 h (formation of the *cis* anhydride is monitored by ^{1}H NMR), then the solvent was evaporated and the residue crystallized from benzene (2 ml) to yield 595 mg of pure **4** (80%). $[\alpha]_D$ +123 (*c* 2.78, EtOH) {lit.[2] $[\alpha]_D$ +160 (*c* 2.7, EtOH.)}; Mp 145–147°C; ^{1}H NMR (200 MHz, $CDCl_3$): 2.1–2.7 (m, 4H), 2.85 (m, 2H, H_1 and H_2), 5.75 (m, 2H, H_4 and H_5), 9.6 (bs, 2H, COOH). ^{13}C NMR (50.3 MHz, $CDCl_3$): 28.5, 42.1, 125.5, 181.5. IR ($CHCl_3$): 3300–2900, 1714. Analysis calcd. for $C_8H_{10}O_4$: C 56.47, H 5.92; found: C 56.25, H 6.09.

The enantiomeric excess of **4** was determined to be 85% by synthesizing the bis-mandelate ester (Scheme 2) according to the reported procedure.[16] ^{1}H NMR (C_6D_6, 200 MHz): 2.18–2.7 (m, 4H), 3.0–3.25 (m, 8H), 5.4 (m, 2H, H_4 and H_5), 6.08 (s, 1H, benzylic proton of the (1*R*,2*R*) diester), 6.11 (s, 1H, benzylic proton of the (1*S*,2*S*) diester), 7.0–7.5 (m, 5H).

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