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threo-3,4-Divinyladipic Acid

Robert B. Grossman†

Department of Chemistry, University of Kentucky,
Lexington, Kentucky 40506-0055

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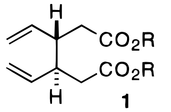
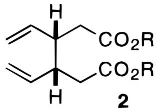
In the course of the synthesis of some C_2-symmetric ligands for transition metals, we required the C_2 (*threo*) isomer of 3,4-divinyladipic acid, **1a**. This compound was reported only once, in 1981, when it was synthesized among several other compounds, including its C_s (*erythro*) isomer **2a**, by the electrocondensation of carbon dioxide and butadiene.[1] We found it surprising that this rather small, functionalized, C_2-symmetric chiral building block had not yet been synthesized in good yield and diastereopure form. We now report the synthesis of **1a**.



1



2

a: R= H
b: R= CH_3
c: R= Et

Our requirement of a diastereoselective route to **1** suggested that we start with *trans*-substituted cyclohexene **3**, easily synthesized on a large scale from the Diels−Alder adduct of butadiene sulfone and diethyl fumarate (Scheme 1).[2] Ozonolysis of **3** at 0 °C followed by $NaBH_4$ reduction gave water-soluble diol **4a** in 89% yield. Tosylation of **4a** to give **4b** proceeded well as long as the mixture was maintained at 0 °C, but even at this temperature some substitution of Cl^- for TsO^- was observed, so the crude **4b** was subjected directly to NaI in refluxing acetone to give analytically pure diiodide **4c** in 77% yield (two steps).

Base-promoted elimination of HI from **4c** to give **5** was expected to be facile, but **4c** was much more prone to undergo substitution (or decomposition) than elimination using a wide variety of bases in various solvents. Prior conversion of the CN groups to CH_2OTHP or CH_2OBz groups did not give a compound with the desired reactivity, either. Other groups have also observed that elimination of HX from a 2-haloethyl group can be exceedingly difficult.[3] We resorted to the selenoxide method to accomplish the elimination. Compound **4c** was converted to the diselenide **4d** using $Ph_2Se_2/NaBH_4$. Compound **4d** was then oxidized with a large excess of H_2O_2 in THF; in situ elimination gave diene **5**. Compound **5** was always contaminated with some of the monoeliminated product **6**, which could be separated by Kugelrohr distillation and subjected to oxidation again to give more **5**. It is known that alkyl selenoxides are reduced back to the selenides by the elimination byproduct PhSeOH.[3] The large excess of H_2O_2 used in this reaction should have solved this problem, but apparently the acidic byproducts of the elimination catalyzed the decomposition of H_2O_2 before oxidation of **4d** and **6** was complete.[4] The relative amounts of **5** and **6** varied from run to run, but the yields of **5** and **6** were typically 50−75% and 5−20%, respectively, after a single oxidation of **4d**.

Finally, **6** was hydrolyzed to give **1a** quantitatively. Compound **1a** was converted to its dimethyl ester **1b** under standard conditions in excellent yield.

A shorter route to **1a** was also explored (Scheme 2). 2,4-Hexadiene-1,6-diol[5] underwent double orthoester−Claisen rearrangement in the presence of triethyl orthoacetate to give, not surprisingly, an inseparable ∼1:1 mixture of **1c** and **2c** in good yield. Hydrolysis of this mixture gave the corresponding acids **1a** and **2a**, which could be separated by fractional crystallization. Unfortunately, the more crystalline isomer was the undesired C_s isomer **2a**, and the desired C_2 isomer **1a** remained in solution along with small amounts of **2a** and minor impurities. The diastereomeric purity of **1a** could be enriched to about 90% after two crystallizations of **2a**. However, with both **1a** and **2a** in hand we were able to confirm that the diastereomers were distinguishable by ^1H NMR, and so we were able to establish the diastereomeric purity of **1a** obtained by the longer route with certainty.

In conclusion, *threo*-3,4-divinyladipic acid, **1a**, has been prepared in diastereomerically pure form for the first time. As the starting material **3** has been prepared in enantiopure form,[6] modification of the described synthesis to prepare enantiopure **1a** should be straightforward. The use of **1a** in the synthesis of chiral metallocene complexes will be reported soon.

Experimental Section

***threo*-3,4-Bis(2-hydroxyethyl)adiponitrile (4a).** A solution of **3** (8.00 g, 50.0 mmol)[2] in CH_3OH (400 mL) was cooled to 0 °C, and O_3 (1 L/min, 80 V) was passed through the solution for 1.5 h, when TLC showed the absence of starting material. While the solution was still cool, $NaBH_4$ (5.69 g, 151 mmol) was slowly added.[7] Much evolution of gas occurred. When the addition was complete, the mixture was allowed to warm to room temperature, and the solvent was mostly evaporated. The residue was dissolved in a small amount of water, diluted with brine, and continuously extracted with CH_2Cl_2 for 2 days. The extract was evaporated to give 8.77 g (44.7 mmol, 89% yield) of **4a** as a white solid, mp 70−71 °C. ^1H NMR (200 MHz, D_2O, reference TSP): δ 4.82 (s, 1H), 3.71 (m, 2H), 2.65 (d, 6.3 Hz, 2H), 2.18 (m, 1H), 1.78 (m, 1H), 1.63 (m, 1H). $^{13}C\{H\}$ NMR (50 MHz, D_2O, reference CH_3OH): δ 120.7, 59.2, 34.3, 32.0, 18.6. IR (KBr): 3311, 2964, 2906, 2243, 1457, 1418, 1063, 1045, 1002 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found: C, 60.92; H, 8.25.

***threo*-3,4-Bis(2-iodoethyl)adiponitrile (4c).** A solution of **4a** (7.86 g, 40.0 mmol) in pyridine (50 mL, 620 mmol) at 0 °C was treated with TsCl (19.06 g, 100 mmol). After 2.5 h, the suspension was poured into a solution of 3 N HCl. An oil separated and solidifed. The solid, **4b**, was collected on a fritted funnel and washed copiously with water, EtOAc, and EtOH. The rinsings were extracted with EtOAc, and the organic layer was shaken with 1 N HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to give additional **4b**. The crude **4b** was dissolved in acetone (400 mL), NaI (51.7 g, 345 mmol) was added, and the mixture was allowed to reflux overnight. After the mixture had cooled, a small amount of Na_2SO_3 was added, followed by water. The mixture became homogeneous. The acetone was evaporated on a rotary evaporator, whereupon a precipitate formed in the aqueous solution. The suspension was filtered, and the solid was washed with H_2O and EtOH. The filtrate gave a little more precipitate when diluted with the

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† rbgros1@pop.uky.edu.

(1) van Tilborg, W. J. M.; Smit, C. J. *Recl.: J. R. Neth. Chem. Soc.* **1981**, *100*, 437.

(2) Krawczyk, A. R.; Jones, J. B. *J. Org. Chem.* **1989**, *54*, 1795.

(3) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

(4) Evolution of gas from the reaction mixture was observed.

(5) The preparation of this compound is described in the supplementary material of Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939.

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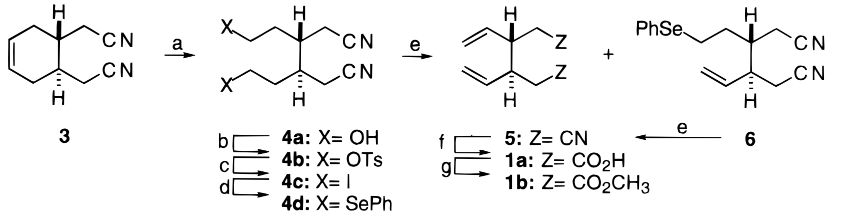
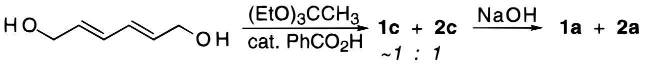
Scheme 1[a]



[a] Key: (a) O_3, MeOH, 0 °C; $NaBH_4$, 89%. (b) TsCl, pyr, 0 °C. (c) NaI, acetone, reflux, 77% (two steps). (d) Ph_2Se_2, $NaBH_4$, THF/ EtOH, 0 °C to rt. (e) Excess H_2O_2, THF, 20 °C, 74% **5,** 5% **6** (2 steps). (f) 3 N aqueous NaOH/ EtOH, reflux, quantitative. (g) CH_3OH, catalytic H_2SO_4, reflux, 88%.

Scheme 2



rinsings, so it was refiltered, and the solid was washed with more H_2O and EtOH. The solids were combined to give 12.76 g (30.7 mmol, 77% yield) of **4c** as an off-white solid, mp 124−125 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 3.35 (dt, $J_d = 10.6$ Hz, $J_t = 6.2$ Hz, 1H), 3.16 (ddd, 6.7 Hz, 8.1 Hz, 10.3 Hz, 1H), 2.49 (m, 2H), 1.9−2.2 (m, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 117.3, 37.9, 33.8, 18.3, 1.8. IR (KBr): 2952, 2887, 2243, 1450, 1415, 1260, 1181, 729, 628, 562 cm^{-1}. Anal. Calcd for $C_{10}H_{14}I_2N_2$: C, 28.87; H, 3.39. Found: C, 28.74; H, 3.33. Note: On larger scales, it is important to free the intermediate ditosylate completely of entrapped pyridine before carrying out the Finkelstein reaction, or considerable material is lost as the pyridinium salt. This can be accomplished by stirring the solid in CH_3OH overnight.

***threo*-3,4-Divinyladiponitrile (5).** A solution of Ph_2Se_2 (9.62 g, 30.8 mmol) in EtOH (150 mL) and THF (75 mL) was cooled to 0 °C under an atmosphere of N_2, and $NaBH_4$ (2.95 g, 78.0 mmol) was added *slowly* in portions. Gas evolved, and the deep yellow color disappeared toward the end of the addition. A solution of **4c** (11.66 g, 28.0 mmol) in THF (250 mL) was added dropwise. When the addition was complete, the mixture was allowed to warm to room temperature. After 3 h, H_2O was added, and the organic solvents were evaporated. The suspension was filtered, rinsing with water and then EtOH to give a white solid, **4d**, which was redissolved in THF (300 mL). A room temperature water bath was placed around the flask. Then 30% aqueous H_2O_2 (25 mL, 230 mmol) was added. Gas evolution began to occur after about 45 min, and the reaction mixture warmed somewhat. The mixture was allowed to stir overnight. The organic solvent was evaporated, and the two-phase mixture was diluted with ether and water and shaken. The organic layer was dried over $MgSO_4$ and evaporated. The material was purified by flash chromatography (20% EtOAc/petroleum ether). The first few fractions yielded recovered Ph_2Se_2; recrystallization from EtOH gave 2.23 g (23% recovery). Fractions containing **5** were combined and evaporated. The orange liquid was subjected to Kugelrohr distillation to give 3.33 g (20.8 mmol, 74% yield) of **5** as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 5.58 (m, 1H), 5.38 (m, 2H), 2.72 (m, 1H), 2.44 (d, 6.8 Hz, 2H). $^{13}C\{H\}$ NMR and APT (50 MHz, $CDCl_3$): δ 132.8 (o), 121.2 (e), 117.6 (q), 43.1 (o), 21.4 (e). IR (neat): 3082, 2985, 2924, 2247, 1640, 1419, 995, 931 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55. Found: C, 74.99; H, 7.25.

The dark orange residue from the distillation was identified as the monoselenide **6** (0.43 g, 1.4 mmol, 5% yield). ^1H NMR (200 MHz, $CDCl_3$): δ 7.51 (m, 2H), 7.30 (m, 3H), 5.57 (dt, $J_d =$ 17.6 Hz, $J_t = 9.2$ Hz, 1H), 5.31 (m, 2H), 3.05 (ddd, 5.1 Hz, 8.2 Hz, 12.4 Hz, 1H), 2.79 (dt, $J_d = 12.5$ Hz, $J_t = 8.0$ Hz, 1H), 2.64 (m, 1H), 2.43 (m, 4H), 2.14 (m, 1H), 1.85 (m, 1H), 1.67 (m, 1H). MS: $M^+ = 318$, 185, 171, 158, 120, 91, 77 (100%), 53; the M^+ peak showed the expected isotopic distribution. This material could be oxidized with H_2O_2 as described above to give more **5**. The relative amounts of **5** and **6** differed from run to run, as did the amount of recovered Ph_2Se_2. Larger-scale runs tended to give less complete oxidation.

***threo*-3,4-Divinyladipic Acid (1a).** A solution of **5** (3.44 g, 21.5 mmol) in 3 N NaOH (ca. 100 mL) and ethanol (ca. 10 mL) was allowed to reflux overnight. The solution was then washed with ether. The aqueous layer was acidified with 3 N HCl, and the solution was then extracted with three portions of CH_2Cl_2. The aqueous layer was then saturated with NaCl and extracted further with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, evaporated, and dried in vacuo to give 4.29 g (21.6 mmol, 101% yield) of **1a** as a white solid, mp 101.5−103 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 11.21 (broad, 1H), 5.62 (m, 1H), 5.14 (m, 2H), 2.73 (~q, 1H), 2.43 (m, 2H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 178.7, 135.9, 118.2, 43.1, 37.5. IR (KBr): 3017 (very broad), 2675, 1707, 1643, 1419, 1301, 1200, 922 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C 60.59, H 7.12. Found: C 60.54, H 7.25.

Dimethyl *threo*-3,4-divinyladipate (1b). A solution of **1a** (4.29 g, 21.6 mmol) in methanol (ca. 100 mL) containing a few drops of concentrated H_2SO_4 was allowed to reflux overnight. The solution was allowed to cool and was quenched with saturated aqueous $NaHCO_3$. The solvent was evaporated, and the residue was taken up in ether and water. The organic layer was shaken with brine, dried over $MgSO_4$, evaporated, and dried in vacuo to give 4.32 g (19.1 mmol, 88% yield) of **1b** as a colorless liquid. ^1H NMR (200 MHz, $CDCl_3$): δ 5.61 (m, 1H), 5.10 (m, 2H), 3.66 (s, 3H), 2.69 (m, 1H), 2.38 (m, 2H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 172.6, 136.5, 117.7, 51.5, 43.6, 37.5. IR (neat): 3078 (w), 2952, 1735 (s), 1639 (w), 1437, 1364, 1259, 1169, 996, 923 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C 63.87, H 8.24.

***erythro*-3,4-Divinyladipic Acid (2a).** A suspension of 2,4-hexadiene-1,6-diol[5] (1.14 g, 10.0 mmol) and pivalic acid (105 mg, 1.03 mmol) in triethyl orthoacetate (18.5 mL, 101 mmol) in a sealed flask was heated to 130 °C for 24 h and then to 145 °C for 24 h.[8] The mixture was diluted with EtOAc, EtOH (20 mL), and 1 N HCl (20 mL) and allowed to stir at room temperature for 1 h. The mixture was then diluted with ether and shaken with saturated aqueous $NaHCO_3$ and then brine. The solution was dried over $MgSO_4$ and evaporated. Flash chromatography (5%, then 6%, then 7% EtOAc in petroleum ether) gave diesters **1c** and **2c** (1.18 g, 4.65 mmol, 47% yield) as an oil contaminated with some unidentified impurities (92% **1c** and **2c** by GC/MS). The ratio **1c**:**2c** was determined to be about 1:1 by examining the relative heights of the (overlapping) CH_3 resonances in the ^1H NMR spectrum. Only slight separation of **1c** and **2c** by GC was seen. ^1H NMR (200 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.10 (m, 2H), 4.21 (two q, 2H), 2.1−2.75 (m, 3H), 1.22 (two t, 3H). MS: $M^+ = 254$, 209, 180, 162, 135, 127, 99, 85, 55.

The mixture of diesters **1c** and **2c** (1.18 g, 4.65 mmol) was suspended in a mixture of 3 N NaOH (20 mL) and EtOH (10 mL), and the mixture was allowed to stir overnight. The solution was acidified with 3 N HCl and extracted three times with EtOAc. The combined organic layers were shaken with brine, dried over $MgSO_4$, and evaporated to give a mixture of diacids **1a** and **2a** (938 mg, 4.73 mmol, 102% yield) as a solid. Recrystallization of the solid from hot H_2O gave flaky white crystals, which were collected by filtration. A second recrystallization gave clean **2a** (305 mg, 1.54 mmol, 33% yield) as flaky white crystals, mp 151.5−153 °C. ^1H NMR (200 MHz, acetone-d$_6$): δ 10.48 (broad, 1H), 5.70 (m, 1H), 5.09 (m, 2H), 2.45−2.60 (m, 2H), 2.15−2.30 (m, 1H). $^{13}C\{H\}$ NMR (50 MHz, acetone-d_6): δ 173.4, 140.1, 117.1, 44.7, 37.6. IR (KBr): 3041 (very broad), 1721, 1654, 1402, 1277, 1159, 923, 677 cm^{-1}. The ^1H NMR spectrum of **2a** showed that a small amount of **1a** (≤3%) was present (δ 2.73, ~q).

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(8) Takano, S.; Sugihara, T.; Ogasawara, K. *Synlett* **1990**, 453.

The mother liquor from the first recrystallization was concentrated, and a second crop of **2a** was obtained. The mother liquor from this recrystallization was then evaporated and dried in vacuo to give **1a** (341 mg, 1.72 mmol, 37% yield) containing some **2a** and an unidentified impurity (^{1}H NMR). This impure **1a** was converted to impure **1b** as described above. The impure **1b** obtained in this way was shown to contain ca. 9% **2b** by integration of the OCH_3 resonances (**1b**, δ 3.66; **2b**, δ 3.63) in the ^{1}H NMR spectrum.

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JO962305V

Additions and Corrections

Vol. 61, 1996

Amit Basu, Donald J. Gallagher, and Peter Beak* . Pathways for Stereoinformation Transfer: Enhanced Enantioselectivity via Diastereomeric Recycling of Organolithium/(−)-Sparteine Complexes.

Pages 5719, Figure 1. The absolute configurations of product **3** are mislabeled. The product on the left section of the energy diagram should be (*S*)-**3**, and the product on the right portion should be (*R*)-**3**. This correction does not affect any of the conclusions of this paper.

JO964031H

S0022-3263(96)04031-5

Rainer Koch, Ming Kah Wong,* and Curt Wentrup*. Facile 1,3- and 1,5-Chlorine Migration.

Page 6809. It has come to our attention that a paper describing related 1,3- and 1,5-*hydrogen* shifts in ketenes and other carbonyl compounds has been published by D. M. Birney (*J. Org. Chem*. **1996**, *61*, 243−251) in which the pseudopericyclic nature of such H-shifts is pointed out, and the effects of geometry, exothermicity of reaction, and electrophilicity and nucleophilicity of the reacting centers are discussed. This paper should have been cited in our article.

JO9740002

S0022-3263(97)04000-0

Fen-Tair Luo* and Li-Chen Hsieh. Palladium-Catalyzed Cross Coupling Reactions of β-Iodo-β,γ-enones with Organozinc Chlorides.

Page 9060, author's address. People's Republic of China should be replaced by Republic of China.

JO974001U

S0022-3263(97)04001-2