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# Enantioselective Synthesis of Dimethyl 3,4-Diphenyladipate by Electroreductive Hydrocoupling of Chiral *N-trans*-Cinnamoyl-2-oxazolidones

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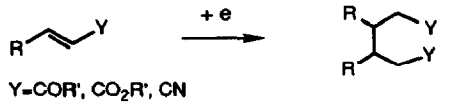
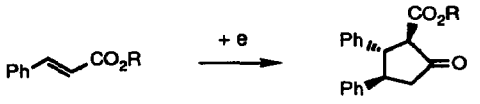
*Abstract:* Dimethyl (*3R,4R*)- and (*3S,4S*)-diphenyladipate were synthesized enantioselectively by electroreductive intermolecular hydrocoupling of chiral *N-trans*-cinnamoyl-2-oxazolidones and subsequent methanolysis.

Electroreductive hydrocoupling of α,β-unsaturated compounds in aqueous solution is well known as a practical method for synthesis of adipic acid derivatives (eq 1).[1] The electroreductive hydrocoupling of β-



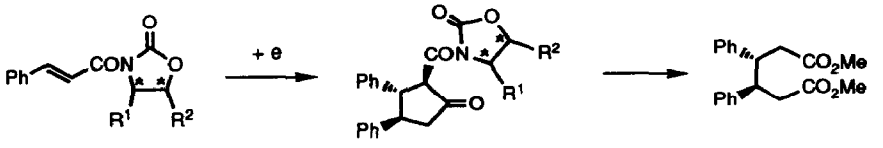

(1)

substituted α,β-unsaturated compounds is, however, usually non-diastereoselective. On the other hand, it has been reported that the electroreduction of cinnamic acid esters in aprotic solution gave cyclized products of hydrodimers[2] and they were obtained as all-*trans* isomers stereospecifically (eq 2).[2a-c] These results prompt us



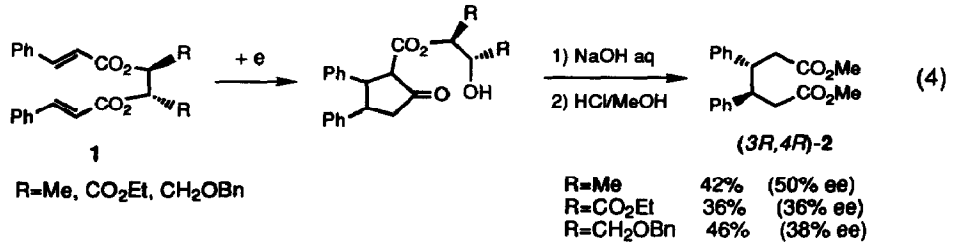

(2)

to investigate enantioselective hydrocoupling of cinnamic acid derivatives. We wish to report herein an enantioselective synthesis of 3,4-diphenyladipic acid utilizing electroreductive intermolecular hydrocoupling of chiral *N-trans*-cinnamoyl-2-oxazolidones (eq 3).



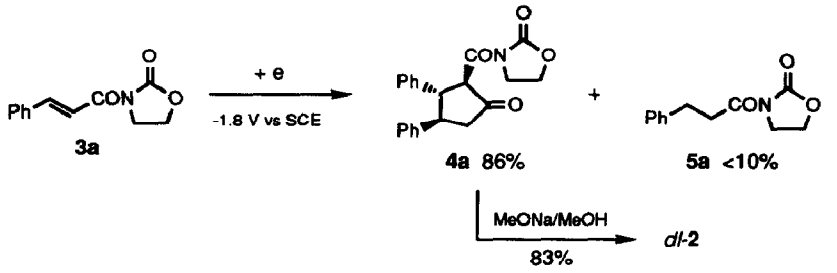

(3)

First, we examined the intramolecular hydrocoupling of chiral diesters **1** prepared from L-tartaric acid derivatives and *trans*-cinnamoyl chloride (2 equiv.). The results of the electroreductive hydrocoupling of some diesters **1** and the subsequent transformation of adducts to dimethyl 3,4-diphenyladipate **2** are shown in eq 4. The material and optical yields of (*3R,4R*)-**2** were, however, not satisfactory.



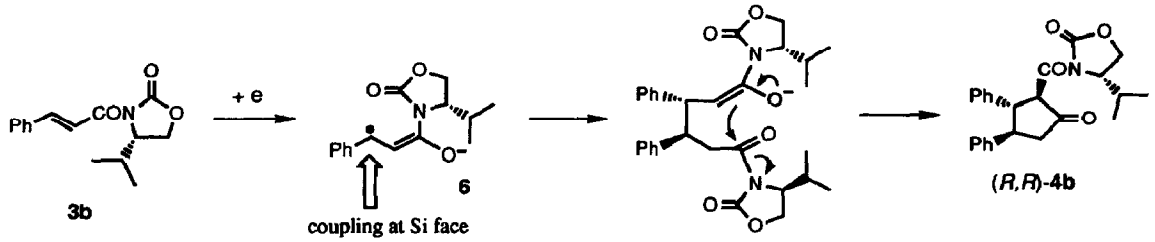

(4)

Next, we studied the intermolecular hydrocoupling of *N-trans*-cinnamoyl-2-oxazolidones **3**.[3] The electroreduction of *N-trans*-cinnamoyl-2-oxazolidone **3a** also yielded hydrocoupling product **4a** as a single stereoisomer together with a small amount of hydrogenated product **5a** (eq 5).[5] The treatment of **4a** with sodium



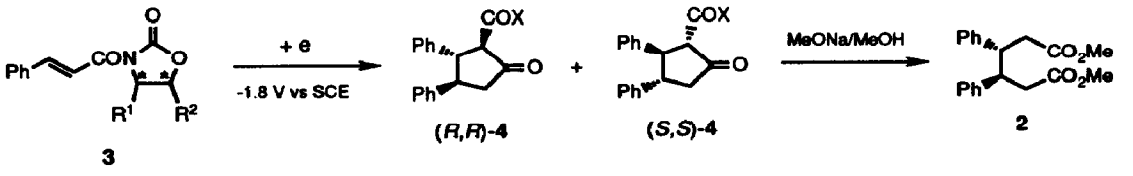

methoxide in methanol gave *dl*-**2**[6] in 83% yield and *meso*-**2** could not be detected. This fact shows that the stereoconfiguration of the two phenyl groups in **4a** is trans. Accordingly, we tried the enantioselective synthesis of **2** by the hydrocoupling of chiral *N-trans*-cinnamoyl-2-oxazolidones **3b-f**. The results of the electroreduction of **3b-f** and the subsequent conversion of adducts **4b-f** to **2** are summarized in Table I. This method afforded chiral **2** in moderate optical yields and starting chiral 2-oxazolidones were recovered (>90% from **3b-f** in two steps). Although the cyclized products **4b-f** were obtained as the mixtures of two diastereoisomers, the stereoisomers of **4b** and **4e** could be separated[7] and therefore optically pure **2**[8] was accessible from each isomer of them. The absolute configuration of chiral **2** was determined by the comparison with the authentic sample of (*3S, 4S*)-**2**.[9]

The reaction mechanism of the hydrocoupling of **3** can be speculated similarly to that reported previously for cinnamic acid esters.[2a,b] The stereoselectivity in the formation of **4b-f** can be explained by the steric interaction between the substituents on oxazolidone rings. In the case of the coupling of **3b** (Scheme I), intermediate anion radical **6** couples each other preferentially at less hindered side (*Si* face = β side) and subsequent cyclization of resulting dimer yields (*R,R*)-**4b**.




**Scheme I**

**Table I.** Enantioselective Synthesis of Dimethyl 3,4-Diphenyladipate 2 by electroreduction of 3




3

| 3 | $R^1$ | $R^2$ | % yield of $4^a$(ds)$^b$ | % yield of $2^c$ | % ee of $2^d$(config.) |
|---|---|---|---|---|---|
| 3b | i-Pr (*S*) | H | 88 (81:19) | 80 | 65 (*R,R*) |
| 3c | i-Bu (*S*) | H | 95 (83:17) | 78 | 70 (*R,R*) |
| 3d | Bn (*S*) | H | 83 (70:30) | 73 | 43 (*R,R*) |
| 3e | Ph (*R*) | H | 81 (68:32) | 30 | 45 (*S,S*) |
| 3e | Me (*S*) | Ph (*R*) | 92 (76:24) | 72 | 50 (*R,R*) |

a. Isolated yields from 3. b. Diastereomeric ratios determined by $^1$H NMR spectra. See ref. 7. c. Isolated yields from diastereomeric mixtures of 4. d. Determined by $^1$H NMR spectra using chiral shift regent Eu(hfc)$_3$.

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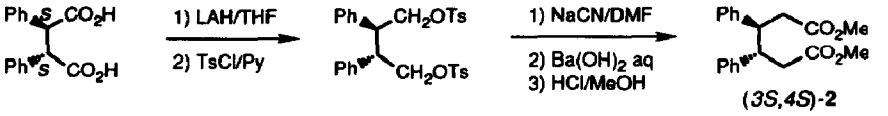
3. The starting materials 3 were prepared from 2-oxazolidones and *trans*-cinnamoyl chloride according to reported method.[4]
4. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
5. General procedure is as follows: A solution of 3 (2 mmol) and Et4NOTs (3 g) in dry acetonitrile (35 ml) was put into a cell (50 ml beaker) equipped with a lead cathode (5 X 10 cm$^2$) and platinum anode (2 X 2 cm$^2$). Electricity was passed at constant potential of -1.8 V vs SCE at room temperature until almost all of 3 was consumed (ca. 400 c). The mixture was poured into water (100 ml) and extracted with dichloromethane. The product 4 was isolated by column chromatography on silica gel. **4a**: *Rf* 0.55 (hexane/ethyl acetate = 1/1); mp 158-160 °C; $^1$H NMR (200 MHz, CDCl3) δ 2.70 (dd, 1 H, J = 12.7 and 19.2 Hz), 3.03 (dd, 1 H, J = 8.1 and 19.2 Hz), 3.44-3.70 (m, 1 H), 3.84-4.19 (m, 3 H), 4.28-4.52 (m, 2 H), 5.35-5.62 (m, 1 H), 7.06-7.32 (m, 10 H); $^{13}$C NMR (50 MHz, CDCl3) δ 42.46 (t), 46.31 (t), 47.66 (d), 52.37 (d), 61.88 (t), 62.17 (d), 127.17 (d), 127.35 (d), 127.55 (d), 127.73 (d), 128.68 (d), 138.80 (s), 139.93 (s), 153.57 (s), 167.77 (s), 208.10 (s).
6. General procedure is as follows: To a solution of sodium methoxide (2.2 mmol) in methanol (20 ml) was added a solution of 4 (1 mmol) in methanol (5 ml) at 0°C and the temperature was allowed to room temperature. After stirring for 8 h, the mixture was neutralized with *1N* HCl and extracted with ether. The product 2 was isolated by column chromatography on silica gel (hexane/ethyl acetate = 7/1). *dl*-2: mp 69-71

°C; $^1$H NMR (200 MHz, $CDCl_3$) δ 2.54-2.81 (m, 4 H), 3.42-3.58 (m, 2 H), 3.55 (s, 6 H), 6.82-6.96 (m, 4 H), 7.10-7.24 (m, 6 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 37.47 (t), 46.14 (d), 51.52 (q), 126.86 (d), 127.98 (d), 128.90 (d), 140.19 (s), 172.76 (s).

7. The cyclized products **4** were obtained as the mixtures of (*R,R*)- and (*S,S*)-**4**. Although the stereoisomers of **4c**, **4d**, and **4f** could not be separated, those of **4b** and **4e** could be isolated by column chromatography on silica gel. (*R,R*)-**4b** (major): *Rf* 0.55 (hexane/ethyl acetate = 2/1); mp 159-161 °C; $[\alpha]^{20}_D$ -59.0 (c 0.5, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3 H, J = 7.0 Hz), 1.01 (d, 3 H, J = 6.7 Hz), 2.25-2.48 (m, 1 H), 2.68 (dd, 1 H, J = 11.7, 19.7 Hz), 3.04 (dd, 1 H, J = 7.7, 19.7 Hz), 3.47-3.68 (m, 1 H), 4.06 (t, 1 H, J = 11.9 Hz), 4.21 (d, 2 H, J = 5.2 Hz), 4.34-4.48 (m, 1 H), 5.52 (d, 1 H, J = 11.9 Hz), 7.10-7.32 (m, 10 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 13.99 (q), 17.46 (q), 27.78 (d), 46.22 (t), 47.28 (d), 51.83 (d), 58.26 (d), 62.33 (d), 62.93 (t), 126.95 (d), 127.12 (d), 127.41 (d), 127.67 (d), 128.51 (d), 138.96 (s), 139.96 (s), 153.85 (s), 167.47 (s), 207.75 (s). (*S,S*)-**4b** (minor): *Rf* 0.50 (hexane/ethyl acetate = 2/1); mp 188-190 °C; $[\alpha]^{20}_D$ +194 (c 0.5, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) δ 0.53 (d, 3 H, J = 6.2 Hz), 0.79 (d, 3 H, J = 7.1 Hz), 2.02-2.25 (m, 1 H), 2.69 (dd, 1 H, J = 10.2, 20.2 Hz), 3.03 (dd, 1 H, J = 8.1, 20.2 Hz), 3.48-3.70 (m, 1 H), 4.04 (t, 1 H, J = 12.0 Hz), 4.17 (dd, 1 H, J = 2.5, 8.2 Hz), 4.32 (t, 1 H, J = 8.2 Hz), 4.39-4.50 (m, 1 H), 5.57 (d, 1 H, J = 12.0 Hz), 7.04-7.48 (m, 10 H), $^{13}$C NMR (50 MHz, $CDCl_3$) δ 13.96 (q), 17.37 (q), 28.16 (d), 46.24 (t), 47.45 (d), 53.13 (d), 58.69 (d), 62.12 (d), 63.27 (t), 127.05 (d), 127.22 (d), 127.44 (d), 128.50 (d), 128.57 (d), 138.36 (s), 139.88 (s), 154.08 (s), 167.92 (s), 208.32 (s). (*S,S*)-**4e** (major): *Rf* 0.55 (hexane/ethyl acetate = 2/1); mp 186-188 °C; $[\alpha]^{20}_D$ -37.0 (c 1.0, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) δ 2.60 (dd, 1 H, J = 12.0, 16.3 Hz), 3.01 (dd, 1 H, J = 12.0, 23.0 Hz), 3.45-3.67 (m, 1 H), 4.00 (t, 1 H, J = 12.1 Hz), 4.21 (dd, 1 H, J = 5.2, 8.8 Hz), 4.63 (t, 1 H, J = 8.8 Hz), 5.33 (dd, 1 H, J = 5.2, 8.8 Hz), 5.50 (d, 1 H, J = 12.1 Hz), 7.02-7.50 (m, 15 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 46.39 (t), 47.47 (d), 51.54 (d), 57.90 (d), 62.49 (d), 69.81 (t), 125.95 (d), 127.08 (d), 127.26 (d), 127.46 (d), 127.78 (d), 128.63 (d), 129.23 (d), 138.,40 (s), 139.02 (s), 139.87 (s), 153.78 (s), 166.90 (s), 207.24 (s). (*R,R*)-**4e** (minor): *Rf* 0.45 (hexane/ethyl acetate = 2/1); mp 168-170 °C; $[\alpha]^{20}_D$ -184 (c.1.0, $CHCl_3$), $^1$H NMR (200 MHz, $CDCl_3$) δ 2.61 (dd, 1 H, J = 12.1, 19.1 Hz), 2.95 (dd, 1 H, J = 8.1, 19.1 Hz), 3.42-3.64 (m, 1 H), 3.88 (t, 1 H, J = 11.8 Hz), 4.07 (dd, 1 H, J = 3.4, 8.8 Hz), 4.62 (t, 1 H, J = 8.8 Hz), 5.38 (dd, 1 H, J = 3.4, 8.8 Hz), 5.60-5.30 (m, 1 H), 6.67-7.23 (m, 15 H), $^{13}$C NMR (50 MHz, $CDCl_3$) δ 46.59 (t), 47.50 (d), 53.52 (d), 57.64 (d), 62.38 (d), 69.87 (t), 125.37 (d), 127.19 (d), 127.34 (d), 127.55 (d), 127.66 (d), 128.53 (d), 128.70 (d), 129.19 (d), 138.33 (s), 138.43 (s), 139.93 (s), 153.84 (s), 168.07 (s), 208.68 (s).
8. Optically pure (*R,R*)- and (*S,S*)-**2** were obtained from (*R,R*)- and (*S,S*)-**4b** (75~80% yields), respectively. (*R,R*)-**2** (>98% ee): $[\alpha]^{20}_D$ +17.4 (c 2.1, $CHCl_3$). (*S,S*)-**2** (>98% ee): $[\alpha]^{20}_D$ -17.3 (c 1.0, $CHCl_3$).
9. The authentic sample of (*3S,4S*)-**2** was prepared from (*2S,3S*)-diphenylsuccinic acid[10] according to the following equation.

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