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Chirality Transfer from Lactic Acid Derivatives via [3,3] Sigmatropic Rearrangements

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Enantiomerically pure lactaldehyde **4** was converted via stereoselective Wittig reactions to the *E* or *Z* enoates **5** or **6**. These were then transformed into the *E* and *Z* allylic trichloroimidates **9** and **13**, respectively. Thermal [3,3] sigmatropic rearrangement of **9** and **13** yielded **10** and **14**, respectively, thus providing a simple entry to both enantiomers of 1,2-amino alcohol derivatives from a single chiral precursor.

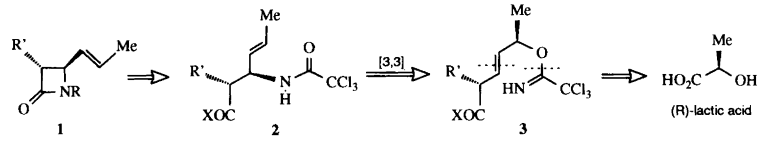
In connection with a project aimed at the enantioselective total synthesis of β-lactam antibiotics,[1] we performed the retrosynthetic analysis shown in Scheme 1.

The key intermediate **2** was thus expected to arise from a [3,3] sigmatropic rearrangement of the allylic trichloroimidate **3**. This reaction[2,3] is synthetically attractive since it is known to proceed with excellent levels of chirality transfer[4] and can be carried out thermally or, under milder conditions, in the presence of metal catalysts.[2b,5] For the present purpose, the required chiral starting material is lactic acid, esters of which are commercially available in both enantiomeric series. In this paper we describe our results with some simpler substrates related to **3**, and compare and contrast our findings with some recently published work.[3g,h]

The high levels of chirality transfer observed in the [3,3] sigmatropic rearrangement of allylic substrates akin to **3** can be attributed to the chair-like six-membered transition states shown in Scheme 2, the substituent R being expected to prefer the 'equatorial' position. In the course of the rearrangement, the original stereogenic centre is destroyed but is used to control the absolute stereochemistry at another site in a process known[6] as 'self-immolative asymmetric synthesis'. Further, as shown in Scheme 2, if the configuration of the original olefinic double bond can be controlled efficiently, then this will provide access to both enantiomers of the product from a single chiral precursor.

The starting material (Scheme 3) was (*R*)-**4** which was readily prepared from commercially available isobutyl (*R*)-(+)-lactate via a procedure described for the enantiomeric aldehyde.[7] It has been demonstrated[7] that no detectable racemization occurs under the conditions used. Our first concern was the above-mentioned control of olefin stereochemistry, and we found that good to excellent stereoselectivity could be attained in the Wittig-type reactions shown below. The *E*:*Z* ratios were determined by integration of the ^{1}H NMR spectra of the crude products, and the isomeric enoates could be separated easily by flash chromatography.

From the enantiomer of **4**, Annunziata *et al.*[8] obtained the antipodes of **5** (*E*:*Z* ratio 14:1) and **6** (*E*:*Z* ratio 1:8), the latter by use of a modification of the procedure of Still and Gennari.[9] The present route to the *Z*-olefin, via Wittig reaction of a stabilized phosphorane in a protic solvent,[10] gives lower stereoselectivity but is still preparatively useful and also experimentally easier to perform. Compounds **5** and **6** were then transformed into **9** and **13**, respectively, via the sequence shown in Scheme 4; reduction[8] of the esters by diisobutylaluminium hydride (DIBAL) gave the corresponding optically pure[11] primary allylic alcohols (**7a**, **11a**) which were protected as the benzyl ethers (**7b**, **11b**) and removal of the silyl protective groups yielded the secondary alcohols (**8**, **12**) which were converted into the allylic trichloroimidates (**9**, **13**). Finally, upon being heated under reflux in xylene, **9** and



Scheme 1.

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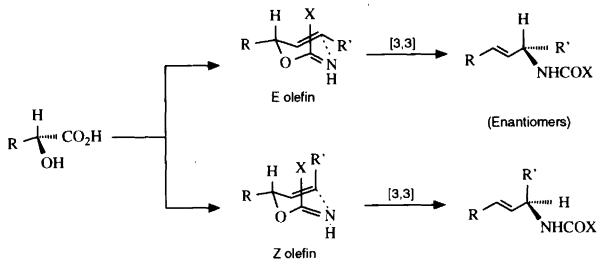
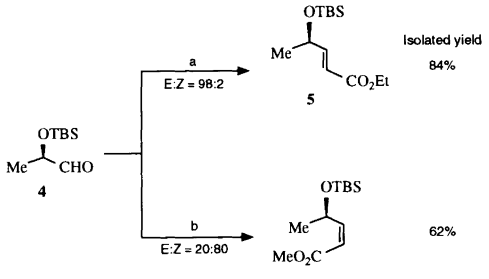


Scheme 2.



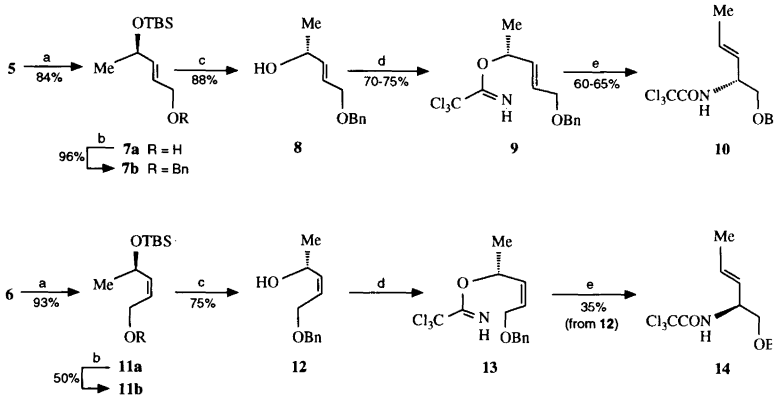
Scheme 3. TBS = Si^{t}BuMe$_2$. (a) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, −30 °C. (b) $Ph_3P{=}CHCO_2Me$, MeOH, room temperature.

13 were transformed smoothly into enantiomers **10** and **14**, respectively. The last three operations could be conveniently carried out without isolation of intermediates.

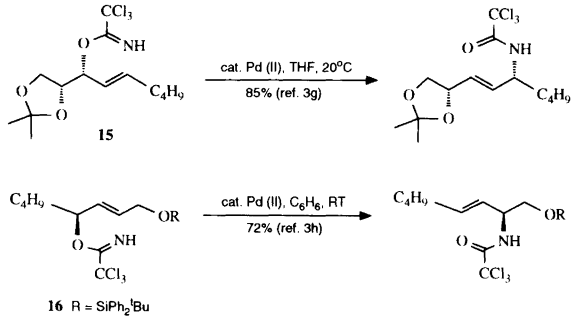
As mentioned above, the [3,3] sigmatropic rearrangement of allylic imidates can often be accelerated by use of metal catalysis particularly by mercury(II) and palladium(II) species[2b,5] but, despite repeated attempts, no rearrangement was observed when **9** was exposed to such catalysts. While the failure of mercuric salts to catalyze the reaction of a secondary allylic alcohol derivative was not surprising,[12] the reluctance of **9** to participate in the palladium-catalyzed process was unexpected. This negative result can be compared with two reports[3g,h] which appeared after our work had been completed (see Scheme 5).

In our hands, exposure of **9** to Pd(II) species in THF at room temperature led only to partial destruction of the substrate, presumably[13] via Pd-catalyzed isomerization of the allylic ether to an enol ether (which was subsequently hydrolyzed upon work-up of the reaction mixture). Although we were aware of this potential problem at the outset, we had not expected enol ether formation to be as rapid as the desired sigmatropic process.[13] The steric bulk of the silyl ether protective group in the closely related **16** presumably hinders formation of the intermediate required for the allylic ether isomerization and allows the [3,3] rearrangement to dominate. Accepting that this protective group is more conducive to the sigmatropic process, it is not difficult to devise suitable modifications[3h] to the reaction sequences shown in Scheme 4. The advantages of the present approach, compared with that described in Ref. 3(h), are that both lactaldehydes are readily available in optically pure form, good to excellent stereocontrol in the Wittig reaction can be achieved simply by changing the reaction conditions, and protected amino acids are easily available from **10** and **14** via cleavage[3a] of the olefinic double bond. Both enantiomers of the product are thus available from a single chiral precursor.

In conclusion, the present combination of stereoselective Wittig reactions and [3,3] sigmatropic rearrangements converts readily available lactates into chiral 1,2-amino alcohol derivatives such as **10** and **14**. These materials are versatile synthetic intermediates for a variety of further transformations, including preparation of chiral aziridines,[1] β-lactams,[1] amino acids,[3a,h] and peptide isosteres.[3f] It is also possible to introduce further stereogenic centres via stereoselective functionalization of the olefinic double bond.[3b,d] Results with the more elaborate imidates shown in Scheme 1 will be reported elsewhere.



Scheme 4. TBS = Si^{t}BuMe$_2$, Bn = CH_2Ph. (a) DIBAL, CH_2Cl_2, −78 °C. (b) For **7b**: NaH, BnBr, THF, reflux. For **11b**: KH, 18-crown-6, BnBr, THF, reflux. (c) Bu_4NF, THF, room temperature. (d) For **9**: KH, Cl_3CCN, Et_2O. For **13**: KH, 18-crown-6, Cl_3CCN, Et_2O. (e) Xylenes, reflux.



Scheme 5.

Experimental

The aldehyde **4** was prepared as described for the enantiomer.[7] The spectroscopic and physical data for our product were identical, except for the sign of specific rotation, with those published.

Ester **5**. Oil-free NaH (0.013 g, 0.53 mmol) was suspended under nitrogen in dry THF (1 ml) and the stirred mixture cooled to −30 °C. A solution of diethyl ethoxycarbonylmethylphosphonate (0.119 g, 0.50 mmol) in THF (1 ml) was added dropwise. The resultant mixture was stirred at −30 °C for 30 min, a solution of aldehyde **4** (0.109 g, 0.50 mmol) in THF (1 ml) was added over a period of 5 min, and the resultant mixture was stirred at −30 °C for an additional 60 min. Water (5 ml) was added and the resultant mixture extracted with ether (2 × 10 ml). The combined organics were dried over magnesium sulfate, and the solvents were removed to give a crude product which was examined by ^{1}H NMR spectroscopy, which showed the *E*:*Z* ratio to be 98:2. Purification by flash chromatography (silica gel, 5% ether–hexane) gave a stereoisomerically pure product (0.109 g, 84%). The spectral data were in excellent agreement with those published for the enantiomer.[8] However, for the enantiomer, Annunziata *et al.* reported[8] $[\alpha]_{436}$ +4.4° while our sample, under identical conditions, showed −15.3°. We repeated our work with (*S*)-**4** and obtained the *E*-ester having +15.2°. Since the value of specific rotation reported by Annunziata *et al.* is in much better agreement with our values for the enantiomers measured at the sodium D line, −4.6° for *R* and +4.5° for *S*, we suggest that there is simply a typographical error in their paper.

Ester **6**. Methyl (triphenylphosphoranylidene)acetate (3.543 g, 10.6 mmol) was dissolved with stirring under nitrogen in dry methanol (11 ml) and the solution cooled to 0 °C. A solution of the aldehyde **4** (2.085 g, 9.6 mmol) in methanol (10 ml) was added dropwise and the resultant mixture was warmed to room temperature and then stirred for 10 h. The solvent was removed *in vacuo*, the residue was taken up in CH_2Cl_2, and the solution washed twice with water. The organic phase was dried over magnesium sulfate, the solvent was removed *in vacuo*, and the crude product was examined by ^{1}H NMR spectroscopy, which showed the *E*:*Z* ratio to be 20:80. Flash chromatography (5% ether–pentane) gave a stereoisomerically pure product (1.453 g, 62%). The spectral and physical data, except for the sign of specific rotation, were in excellent agreement with those published for the enantiomer.[8]

Allylic alcohol **7a**. Ester **5** (0.892 g, 3.5 mmol) was dissolved with stirring under nitrogen in dry CH_2Cl_2 (10 ml) and the solution cooled to −78 °C. A 1 M solution of DIBAL (in hexanes, 8.6 ml, 8.6 mmol) was added dropwise, and the resultant mixture was stirred at −78 °C until TLC analysis indicated complete consumption of the starting material. The reaction was quenched by careful addition of methanol and the mixture was allowed to reach room temperature while being vigorously stirred. The mixture was filtered through Celite and the filtercake was washed thoroughly with fresh CH_2Cl_2. The combined filtrate and washings were evaporated to dryness and the residue was purified by flash chromatography (30% ether–pentane) to give **7a** (0.624 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$–TMS): δ 5.79 (1 H, dt, J = 15.5, 5, C*H*CH_2OH), 5.71 (1 H, dd, J = 15.5, 4, C*H*=CHCH_2OH), 4.33 (1 H, m, CHOSi), 4.14 (2 H, br dd, J = 6, 5, CH_2OH), 1.33 (1 H, br t, J = 6, OH), 1.22 (3 H, d, J = 6.5, Me), 0.90 (9 H, s, ^{t}BuSi), 0.09 (3 H, s, MeSi), 0.08 (3 H, s, MeSi). IR: 3330 cm^{-1} (br, s, OH). $[\alpha]_D^{20}$ −3.37° (*c* 1.04, CH_2Cl_2). Anal. $C_{11}H_{24}O_2Si$: C, H.

Benzyl ether **7b**. A suspension of oil-free NaH (0.113 g, 3.8 mmol) was stirred under nitrogen in dry THF (20 ml) and cooled to 0 °C before the dropwise addition of a solution of **7a** (0.673 g, 3.1 mmol) in THF (3 ml). The resultant solution was stirred at 0 °C for 20 min, benzyl bromide (0.7 ml, 4 mmol) was added, and the mixture was heated under reflux for 4 h. The mixture was cooled in an ice-bath and water (10 ml) was added carefully, followed by ether (40 ml). The organic phase was washed twice with water and dried over magnesium sulfate, the solvents were removed *in vacuo*, and the residue was purified by flash chromatography (20% ether–pentane) to give **7b** (0.921 g, 96%). ^{1}H NMR: 7.35 (5 H, m, phenyl), 5.76 (1 H, dd, J = 15.5, 4, C*H*=C*H*CH_2O), 5.71 (1 H, dt, J = 15.5, 4, C*H*CH_2O), 4.50 (2 H, s, CH_2Ph), 4.33 (1 H, m, CHOSi), 4.03 (2 H, m, CH_2OCH_2Ph), 1.22 (3 H, d, J = 6.5, Me), 0.89 (9 H, s, ^{t}BuSi), 0.05 (6 H, 2 × s, Me_2Si). ^{13}C NMR (75 MHz): δ 138.34, 137.97, 128.34, 127.74, 127.53, 124.65, 71.86, 70.24, 68.59, 25.88, 24.35, 18.27. $[\alpha]_D^{20}$ +1.89° (*c* 1.11, CH_2Cl_2). Anal. $C_{18}H_{30}O_2Si$: C, H.

Allylic alcohol **8**. Silyl ether **7a** (0.876 g, 2.9 mmol) was dissolved with stirring under nitrogen in dry THF (3 ml) and the solution cooled to 0 °C. A solution of Bu_4NF (1.1 M in THF, 4.4 ml, 4.9 mmol) was added dropwise, the resultant mixture was allowed to reach room temperature, and stirring was continued overnight. The mixture was diluted with ether (20 ml) and then washed

twice with water. The organic phase was dried over magnesium sulfate, the solvents were removed *in vacuo*, and the residue was purified by flash chromatography (75% ether–pentane) to afford **8** (0.484 g, 88%). ^{1}H NMR: δ 7.30 (5 H, m, phenyl), 5.80 (2 H, m, $J_{trans}=16$, vinyl), 4.51 (2 H, s, CH_2Ph), 4.34 (1 H, m, CHOH), 4.01 (2 H, m, CH_2OCH_2Ph), 1.60 (1 H, br s, OH), 1.28 (3 H, d, $J=6.3$, Me). ^{13}C NMR: δ 134.93, 133.87, 125.16, 124.53, 124.41, 122.99, 69.09, 66.87, 65.01, 19.92. IR: 3390 (br, s, OH). $[\alpha]_D^{20}$ −1.06° (*c* 1.04, CH_2Cl_2). Anal. $C_{12}H_{16}O_2$: C, H.

Trichloroimidate **9**. Oil-free KH (0.420 g, 1.1 mmol) was suspended in dry ether (1 ml) under nitrogen and stirred at room temperature. A solution of the alcohol **8** (0.135 g, 0.7 mmol) in ether (1 ml) was added rapidly in one portion, and the resultant yellow solution was stirred for 15 min and cooled to −15 °C before the slow dropwise addition of a solution of freshly distilled trichloroacetonitrile (0.112 g, 0.77 mmol) in ether (1 ml). The resultant brown solution was stirred at −15 °C for 1 h and then at room temperature for an additional 3 h. Hexane (1 ml) and methanol (0.3 ml) were added, and the resultant mixture was filtered through a pad of Celite. The solvents were removed *in vacuo* at room temperature to yield the crude trichloroimidate which was pure according to NMR spectroscopy and was used directly in the next step. (Attempted purification by flash chromatography led to extensive decomposition, and Kugelrohr distillation resulted in partial rearrangement to **10**). Yields were typically 70–75% of material sufficiently pure for the next step. ^{1}H NMR: δ 7.32 (5 H, m, phenyl), 5.87 (1 H, dt, $J=15.4$, 6, $CHCH_2O$), 5.76 (1 H, dd, $J=15.4$, 7, $CH=CHCH_2O$), 5.21 (1 H, quintet, $J=7$, CHOC=N), 4.50 (2 H, s, CH_2Ph), 4.01 (2 H, m, CH_2OCH_2Ph), 1.38 (3 H, d, $J=7$, Me). IR: 1660 (s, C=N).

Trichloroacetamide **10**. The crude trichloroimidate from above was taken up in xylenes (2 ml) and heated at reflux under nitrogen for 12 h, the progress of the reaction being monitored by TLC. The solvent was removed *in vacuo* and the residue was purified by flash chromatography. Yields were typically ca. 45% for the two steps from **8**. (It was also found that purification of **8** was not usually necessary and the conversion of **7b** into **10** could thus be carried out without isolation of intermediates). ^{1}H NMR: δ 7.32 (5 H, m, phenyl), 7.06 (1 H, br d, $J=7$, NH), 5.76 (1 H, dqd, $J=15$, 6.5, 1, $CH_3CH=C$), 5.52 (1 H, ddq, $J=15$, 6, 1.9, $CH_3CH=CH$), 4.57 (2 H, s, CH_2Ph), 4.51 (1 H, m, $CHCH_2O$), 3.62 (1 H, dd, $J=9.5$, 4, $CHOCH_2$Ph), 3.56 (1 H, dd, $J=9.5$, 4, $CHOCH_2$Ph), 1.71 (3 H, dd, $J=6.5$, 1.9, Me). ^{13}C NMR: δ 161.12, 137.52, 129.17, 128.51, 127.93, 127.72, 126.70, 92.70, 73.27, 71.11, 52.79, 17.85. (The CCl_3 signal at 92.70 was sometimes too weak to be observed). IR: 3420 and 3350 (w, N–H), 1721 (s, C=O), 1506 (s, CO–NH–). $[\alpha]_D^{20}$ +10.32° (*c* 0.98, CH_2Cl_2). Anal. $C_{14}H_{16}Cl_3NO_2$: C, H.

Allylic alcohol **11a**. This was prepared from **6** using the method described above for **7a**. On a 10 mmol scale, the isolated yield was 93%. ^{1}H NMR: δ 5.60–5.47 (2 H, m, $J_{cis}=11$, vinyl), 4.58 (1 H, quintet, $J=6$, CHOSi), 4.26 (1 H, m, CHO), 4.14 (1 H, m, CHO), 1.89 (1 H, br m, OH), 1.21 (3 H, d, $J=6$, Me), 0.90 (9 H, s, ^{t}BuSi), 0.07 (6 H, 2 × s, Me_2Si). IR: 3330 (br, s, OH). $[\alpha]_D^{20}$ −25.54° (*c* 1.01, CH_2Cl_2).

Benzyl ether **11b**. The procedure described for **7b** was modified as follows. The alcoholate of **11a** was generated using KH in THF, and a catalytic amount of 18-crown-6 was added before the addition of benzyl bromide. The reaction mixture was heated under reflux for 24 h before being worked up as described above. Isolated yields were usually ca. 50%, the mass balance being recovered starting material. ^{1}H NMR: δ 7.36 (5 H, m, phenyl), 5.61 (1 H, ddq, $J=11$, 7.5, 1, $CH=CHCH_2O$), 5.50 (1 H, dt, $J=11$, 6, $CH=CHCH_2O$), 4.55 (1 H, m, CHOSi), 4.51 (2 H, AB, $J=10$, CH_2Ph), 4.15–4.01 (2 H, m, CH_2OCH_2Ph), 1.19 (3 H, dd, $J=7$, 1, Me), 0.88 (9 H, s, ^{t}BuSi), 0.03 (6 H, 2 × s, Me_2Si). ^{13}C NMR: δ 138.22, 138.16, 128.38, 127.72, 127.63, 124.33, 72.34, 65.92, 65.17, 25.81, 24.73, 18.15. $[\alpha]_D^{20}$ −23.17° (*c* 1.01, CH_2Cl_2).

Allylic alcohol **12**. This was prepared from **11b** according to the procedure described above for **8**. The isolated yield was usually ca. 75%. ^{1}H NMR: δ 7.33 (5 H, m, phenyl), 5.65 (2 H, m, $J_{cis}=11$, vinyl), 4.58 (1 H, m, CHOH), 4.53 (2 H, s, CH_2Ph), 4.16 (1 H, m, $J_{gem}=11.5$, $CHOCH_2$Ph), 4.05 (1 H, m, $CHOCH_2$Ph), 2.05 (1 H, br m, OH), 1.24 (3 H, d, $J=6.8$, Me). ^{13}C NMR: δ 137.84, 137.64, 128.45, 127.82, 127.78, 126.76, 72.49, 65.68, 63.92, 23.29. IR: 3395 (br, s, OH). $[\alpha]_D^{20}$ +0.48° (*c* 1.05, CH_2Cl_2).

Trichloroacetamide **14**. This was prepared from **12** as described for **10**, with the exception that a catalytic amount of 18-crown-6 was used in the preparation of the trichloroimidate (IR: 1662 cm^{-1}) which was used directly in the sigmatropic rearrangement reaction. The overall yield of **14** from **12** was ca. 35%, and the final product, which showed $[\alpha]_D^{20}$ −10.9° (*c* 1.13, CH_2Cl_2), was chromatographically and spectroscopically indistinguishable from **10**.

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