Total Syntheses of (+)- and (–)-Nonactate Esters using Silicon Compounds to Control the Stereochemistry

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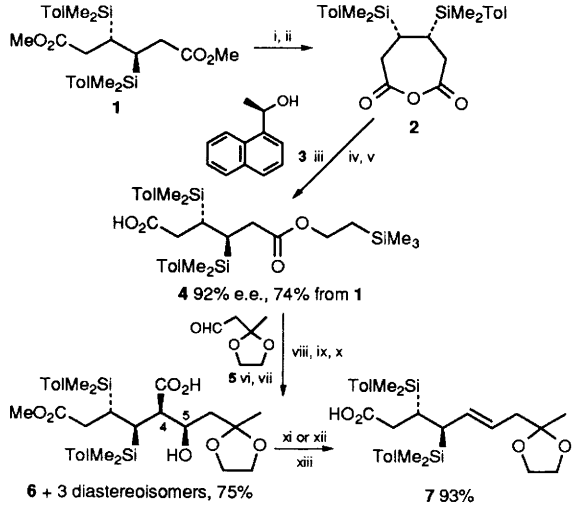
1,3-Transposition, using the epoxidation of the allylsilane **7**, derived from the meso 3,4-disilylated adipate **1**, gives the 1,4-related stereocentres of 8-oxo-6-hydroxy-3-dimethyl(tolyl)silylnonanoic acid ethylene acetal **10**; two highly stereocontrolled sequences from this common intermediate give methyl (+)-nonactate **13** and benzyl (–)-nonactate **17**.

Nonactic acid and its derivatives, such as the methyl ester **13**, with four stereogenic centres having 1,2-, 1,3- and 1,4-relationships, have been popular targets for demonstrating new methods of stereocontrol.[1–4] We have developed versatile methods, using organosilicon chemistry, to control 1,2- and 1,3-related centres,[5] like those in nonactic acid, but hitherto we have had no method for the 1,4-related centres that it challenged us to. We now report a synthesis of the homochiral 6-hydroxy-3-silylnonanoic acid **10**, having 1,4-related stereocentres, and the conversion of this common intermediate into the nonactate esters **13** and **17**, one in each enantiomeric series, illustrating the versatility of our silicon-based methods of stereocontrol.[6]

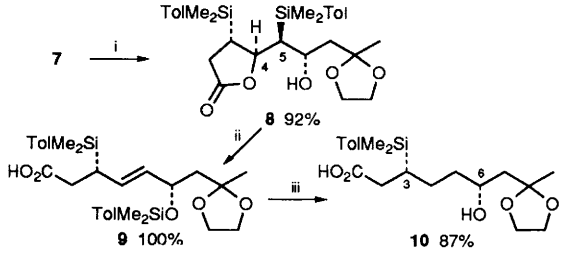
We reported earlier[7] an efficient and completely stereoselective synthesis of the 3,4-disilylated adipic ester **1** from the corresponding methyl β-silylacrylate, using Inanaga's samarium(II) coupling.[8] We converted this meso diester into the meso anhydride **2**, and opened it with Heathcock's homochiral alcohol **3**,[9] enriched to a high level (99.7% e.e.) of enantiomeric purity by Horeau's method,[10] as already reported.[11] The inseparable diastereoisomeric esters were present in a ratio of 96:4, and gave therefore the homochiral mono ester **4** in 92% e.e. Using one of our allylsilane syntheses,[12] we converted this ester into the *E*-allylsilane **7**. In the first step, aldol condensation with Kelly's aldehyde **5**[13] gave largely the diastereoisomer **6**, but with all four possible isomers detectable in a ratio of 76:9:9:6. We separately treated the two diastereoisomers with a *syn* relationship between the substituents on C-4 and C-5 (the 76% and 9%) with benzenesulfonyl chloride, and heated the derived β-lactone to induce a *syn* stereospecific decarboxylative elimination, and, without separating them from each other, we treated the two with an *anti* relationship with dimethylformamide dineopentyl acetal to induce an *anti* stereospecific decarboxylative elimination. This is the first time that we have used the full convergent possibilities of this synthetic method, and the overall yield of the *E*-allylsilane **7** from the ester **4** was a gratifying 68% (Scheme 1).

Epoxidation of the allylsilane (Scheme 2), a reaction known to be stereospecifically *anti*,[14] gave the lactone **8** as a consequence of precedented[15] silyl migration from C-4 to C-5. The selective elimination of the silyl group on C-5 and the lactone oxygen on C-4 took place on treatment with potassium hydride, with both the chemoselectivity and the stereoselectivity for the *trans* product **9** having good precedent in the work of Yamamoto.[16] Hydrogenation of this silyl ether to give the key intermediate **10** took place only after the *O*-silyl group had been removed, in line with earlier difficulties we have had in trying to hydrogenate allylsilanes. Thus we had controlled the 1,4-related centres between C-3 and C-6, in 12 steps, in an overall yield of 40% from the ester **1**.

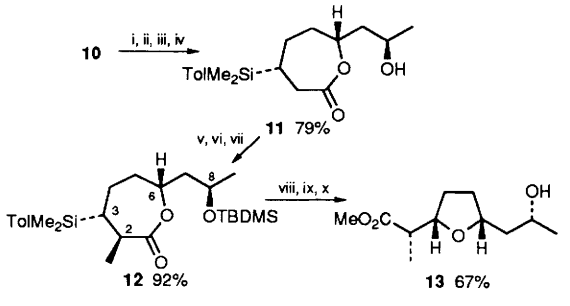
From this branch point, we carried out two sequences to give each of the nonactate esters. In the first (Scheme 3), we used Evans' method[17] for reducing a 3-hydroxyketone to an *anti* 1,3-diol (*ca.* 95:5), which we separated and treated with Mukaiyama's reagent[18] to give the lactone **11**. At this stage we were able to filter off a small amount of the crystalline racemic



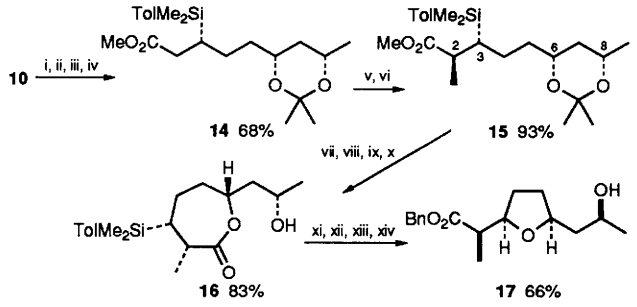
Scheme 1 *Reagents and conditions*: i, LiOH, THF, MeOH, H_2O, room temp., 48 h; ii, DCC, CH_2Cl_2, room temp., 12 h; iii, DMAP, CH_2Cl_2, −30 °C, 4 d; iv, $HOCH_2CH_2SiMe_3$, DCC, DMAP, room temp., 12 h; v, H_2, Pd/C, EtOAc, room temp., 7 d; vi, 2LDA, THF, DMPU, −78 → −50 °C; vii, −78 °C, 2.5 h; viii, CH_2N_2; ix, separate diastereoisomers; x, TBAF, THF, 0 °C → room temp., 0.5 h; xi, (*a*) $PhSO_2Cl$, Py, 0 °C, 20 h (*b*) collidine, reflux, 14 h; xii, $Me_2NCH(OCH_2Bu^t)_2$, $CHCl_3$, reflux, 7 h; xiii, KOH, MeOH, THF, H_2O, 45 °C, 10 h



Scheme 2 *Reagents and conditions*: i, MCPBA, Na_2HPO_4, CH_2Cl_2, room temp., 12 h; ii, KH, THF, 78 °C → 0 °C, 5 h, iii, H_2, PtO_2, MeOH, room temp., 50 h



Scheme 3 *Reagents and conditions*: i, PyH, OTs, Me_2CO, H_2O, reflux, 7 h; ii, Me_4N, $BH(OAc)_3$, AcOH, MeCN, −25 °C, 48 h; iii, 2-chloro-*N*-methylpyridinium iodide, Et_3N, CH_2Cl_2, reflux, 10 h; iv, separate from racemate (92% e.e. → 99% e.e.); v, TBDMSCl, DMF, imidazole, room temp. 15 h; vi, LDA, THF, DMPU, −78 °C, 1 h; vii, MeI, −78 °C, 36 h, −10 °C, 8 h; viii, KBr, AcO_2H, NaOAc, AcOH, room temp., 15 h; ix, TsCl, Py, DMAP, room temp., 5 d; x, TsOH, MeOH, room temp., 4 d



Scheme 4 *Reagents and conditions*: i, CH_2N_2; ii, PyH, OTs, Me_2CO, H_2O, reflux, 2.5 h; iii, $NaBH_4$, Bu_2BOMe, THF, MeOH, −78 °C, 15 h; iv, PyH, OTs, $Me_2C(OMe)_2$, room temp., 15 h; v, LDA, THF, DMPU, −78 °C, 1 h; vi, MeI, −78 °C, 36 h, 10 °C, 8 h; vii, PyH, OTs, MeOH, reflux, 2.5 h; viii, KOH, THF, MeOH, H_2O, 40 °C, 15 h; ix, 2-chloro-*N*-methylpyridinium iodide, Et_3N, CH_2Cl_2, reflux, 10 h; x, separate from racemate (92% e.e. → 96% e.e.); xi, TBDMSCl, DMF, imidazole, room temp., 15 h; xii, $NaOCH_2Ph$, $PhCH_2OH$, THF, room temp., 6 h; xiii, TsCl, Py, DMAP, room temp., 2 d; xiv, KBr, AcO_2H, AcOH, room temp., 15 h

lactone, and thereby raised the e.e. from 92 to 99%. Protection of the free hydroxy group and methylation gave only the lactone **12** with the *anti* relationship between the silyl and methyl groups. Although most of our work on silicon-controlled enolate alkylations has been with open chain esters,[19] we have seen a highly diastereoselective methylation of a caprolactone before.[20] The four stereocentres C-2, C-3, C-6 and C-8 were now in place, all that remained was to convert the silyl to a hydroxy group,[21] to tosylate the new hydroxy group, and open the lactone, whereupon cyclisation took place with inversion of configuration at C-3 to give methyl (+)-nonactate **13**, identifiably the correct diastereoisomer by its definitive[2] ^{1}H NMR spectrum, and with specific rotation, $[\alpha]_D^{22}$ +22.55 (*c* 1.14, $CHCl_3$), close to that reported, $[\alpha]_D^{25}$ +22.1 (*c* 0.7, $CHCl_3$).[4] GC on a homochiral column confirmed the high enantiomeric purity of this material (99.2% e.e.). The overall yield for the 10 steps from the common intermediate **10** to methyl (+)-nonactate **13** was 49%.

In the second sequence (Scheme 4) starting from the 3-hydroxyacetal **10**, we did everything in the opposite sense. We used Prasad's version[22] of Narasaka's method[23] to give the *syn* 1,3-diol (90:10), which we separated from the minor diastereoisomer and protected it as its acetonide **14**. We methylated the ester stereoselectively **14** → **15**, following our well-established rule for the alkylation of open-chain esters having a β-silyl group.[19] Methylation in an open-chain ester sets up the C-2 and C-3 stereocentres in the opposite sense along the carbon backbone to the methylation of the lactone **11** → **12**, although the cause, electrophilic attack taking place *anti* to the silyl group, is of course the same. Acetal hydrolysis, ester hydrolysis and lactonisation gave the lactone **16**, and again some of the crystalline racemate could be filtered off, raising the enantiomeric purity from 92 to 96% e.e. or better. Protection of the free hydroxy group and base-catalysed opening of the lactone with benzyl alcohol revealed the C-6 hydroxy group, which we tosylated to give the benzyl ester. Silyl-to-hydroxy conversion[21] allowed the formation, with inversion of configuration at C-6, of benzyl (−)-nonactate **17**. Hydrogenolysis and treatment with diazomethane gave methyl (−)-nonactate, which appeared to be diastereomerically pure in its ^{1}H NMR spectrum, and enantiomerically pure (although we had calculated that it ought to be 96% e.e.) on the homochiral GC column. The overall yield for the 12 steps from the common intermediate **10** to benzyl (−)-nonactate **17** was 35%.

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