

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

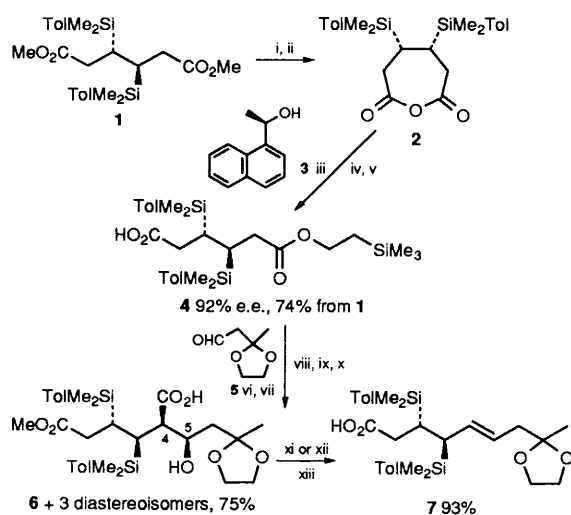
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1,3-Transposition, using the epoxidation of the allylsilane **7**, derived from the meso 3,4-disilylated adipate **1**, gives the 1,4-related stereocentres of 8-oxo-6-hydroxy-3-dimethyl(tolyl)silylnonanoic acid ethylene acetal **10**; two highly stereocontrolled 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.<sup>1–4</sup> We have developed versatile methods, using organosilicon chemistry, to control 1,2- and 1,3-related centres,<sup>5</sup> 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.<sup>6</sup>

We reported earlier<sup>7</sup> an efficient and completely stereoselective synthesis of the 3,4-disilylated adipic ester **1** from the corresponding methyl  $\beta$ -silylacrylate, using Inanaga's samarium(II) coupling.<sup>8</sup> We converted this meso diester into the meso anhydride **2**, and opened it with Heathcock's homochiral alcohol **3**,<sup>9</sup> enriched to a high level (99.7% e.e.) of enantiomeric purity by Horeau's method,<sup>10</sup> as already reported.<sup>11</sup> 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,<sup>12</sup> we converted this ester into the *E*-allylsilane **7**. In the first step, aldol condensation with Kelly's aldehyde **5**<sup>13</sup> 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  $\beta$ -lactone to induce a *syn* stereospecific decarboxylative elimination, and, without separating them from each other, we treated the two with an *anti*

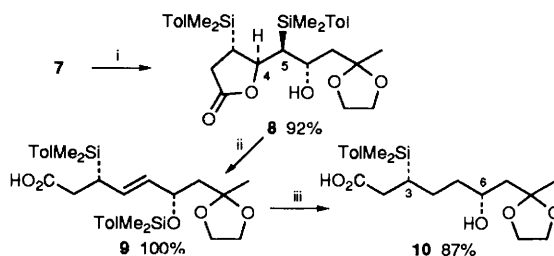


**Scheme 1** Reagents and conditions: i, LiOH, THF, MeOH, H<sub>2</sub>O, room temp., 48 h; ii, DCC, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 12 h; iii, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, –30 °C, 4 d; iv, HOCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>, DCC, DMAP, room temp., 12 h; v, H<sub>2</sub>, Pd/C, EtOAc, room temp., 7 d; vi, 2LDA, THF, DMPU, –78 °C → –50 °C; vii, –78 °C, 2.5 h; viii, CH<sub>2</sub>N<sub>2</sub>; ix, separate diastereoisomers: x, TBAF, THF, 0 °C → room temp., 0.5 h; xi, (a) PhSO<sub>2</sub>Cl, Py, 0 °C, 20 h (b) collidine, reflux, 14 h; xii, Me<sub>2</sub>NCH(OCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>, CHCl<sub>3</sub>, reflux, 7 h; xiii, KOH, MeOH, THF, H<sub>2</sub>O, 45 °C, 10 h

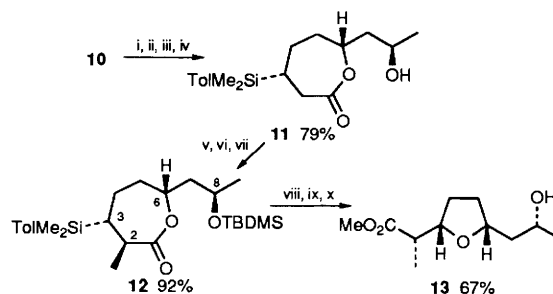
relationship with dimethylformamide dineopentyl acetal to induce an *anti* stereospecific decarboxylative elimination. This is the first time that we have used the full convergent possibilities of this synthetic method, and the overall yield of the *E*-allylsilane **7** from the ester **4** was a gratifying 68% (Scheme 1).

Epoxidation of the allylsilane (Scheme 2), a reaction known to be stereospecifically *anti*,<sup>14</sup> gave the lactone **8** as a consequence of precededented<sup>15</sup> 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.<sup>16</sup> 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**.

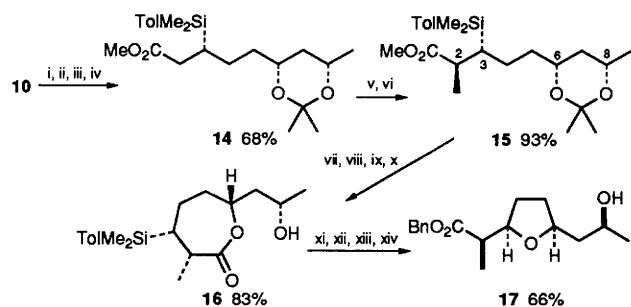
From this branch point, we carried out two sequences to give each of the nonactate esters. In the first (Scheme 3), we used Evans' method<sup>17</sup> for reducing a 3-hydroxyketone to an *anti* 1,3-diol (*ca.* 95:5), which we separated and treated with Mukaiyama's reagent<sup>18</sup> to give the lactone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



**Scheme 2** Reagents and conditions: i, MCPBA, Na<sub>2</sub>HPO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 12 h; ii, KH, THF, 78 °C → 0 °C, 5 h; iii, H<sub>2</sub>, PtO<sub>2</sub>, MeOH, room temp., 50 h



**Scheme 3** Reagents and conditions: i, PyH, OTs, Me<sub>2</sub>CO, H<sub>2</sub>O, reflux, 7 h; ii, Me<sub>2</sub>N, BH(OAc)<sub>3</sub>, AcOH, MeCN, –25 °C, 48 h; iii, 2-chloro-*N*-methylpyridinium iodide, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>H, 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,  $\text{CH}_2\text{N}_2$ ; ii, PyH, OTs,  $\text{Me}_2\text{CO}$ ,  $\text{H}_2\text{O}$ , reflux, 2.5 h; iii,  $\text{NaBH}_4$ ,  $\text{Bu}_2\text{BOMe}$ , THF, MeOH,  $-78^\circ\text{C}$ , 15 h; iv, PyH, OTs,  $\text{Me}_2\text{C}(\text{OMe})_2$ , room temp., 15 h; v, LDA, THF, DMPU,  $-78^\circ\text{C}$ , 1 h; vi, MeI,  $-78^\circ\text{C}$ , 36 h,  $10^\circ\text{C}$ , 8 h; vii, PyH, OTs, MeOH, reflux, 2.5 h; viii, KOH, THF, MeOH,  $\text{H}_2\text{O}$ ,  $40^\circ\text{C}$ , 15 h; ix, 2-chloro-*N*-methylpyridinium iodide,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , reflux, 10 h; x, separate from racemate (92% e.e.  $\rightarrow$  96% e.e.); xi, TBDMSCl, DMF, imidazole, room temp., 15 h; xii,  $\text{NaOCH}_2\text{Ph}$ ,  $\text{PhCH}_2\text{OH}$ , THF, room temp., 6 h; xiii, TsCl, Py, DMAP, room temp., 2 d; xiv, KBr,  $\text{AcO}_2\text{H}$ , 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,<sup>19</sup> we have seen a highly diastereoselective methylation of a caprolactone before.<sup>20</sup> 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,<sup>21</sup> 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  $^1\text{H}$  NMR spectrum, and with specific rotation,  $[\alpha]_{\text{D}}^{22} +22.55$  (*c* 1.14,  $\text{CHCl}_3$ ), close to that reported,  $[\alpha]_{\text{D}}^{25} +22.1$  (*c* 0.7,  $\text{CHCl}_3$ ).<sup>4</sup> 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<sup>22</sup> of Narasaka's method<sup>23</sup> 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**  $\rightarrow$  **15**, following our well-established rule for the alkylation of open-chain esters having a  $\beta$ -silyl group.<sup>19</sup> 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**  $\rightarrow$  **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<sup>21</sup> 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  $^1\text{H}$  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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