Iterative Synthesis

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Asymmetric Conjugate Silyl Transfer in Iterative Catalytic Sequences: Synthesis of the C7–C16 Fragment of (+)-Neopeltolide**

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The assembly of recurring structural motifs in complex molecules, such as 1,3,…*n*-polymethylated or 1,3,…*n*-polyhydroxylated carbon chains (n = odd integers), is elegantly realized by several unique iterative sequences.[1] These approaches enable the stereoselective synthesis of either Me,Me[2–5] or OH,OH[6] (**I** and **II**; Figure 1) but not Me,OH (or OH,Me) arrangements (**III**; Figure 1). We thus sought a flexible strategy that would allow for the direct introduction of either methyl or hydroxy groups into a linear carbon chain. The idea was to merge our enantioselective conjugate silyl transfer[7,8] into the Feringa–Minnaard approach, which hinges upon the repeated catalyst-controlled 1,4-addition of Grignard reagents.[4] Tamao–Fleming oxidative degradation of the carbon–silicon bond[10] in the thus-formed Me,*Si* building block **IV** renders it a synthetic equivalent of the desired unit **III** (Figure 1).

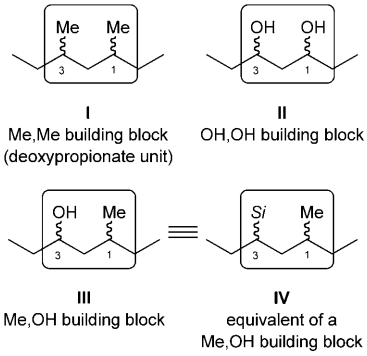

Figure 1. Me,Me and OH,OH and Me,OH building blocks. *Si* = Me_2PhSi.

Herein, we detail the realization of a conjugate addition-based iterative strategy with optional stereocontrolled introduction of either methyl or silyl (hydroxy equivalent) groups into a carbon chain. Aside from the systematic investigation of all isomeric Me,*Si* and *Si*,Me arrangements, we demonstrate the feasibility of our approach in the synthesis of the C7–C16 fragment of (+)-neopeltolide[11] (**1**; Figure 2).[12–14] Protected **2** is an intermediate previously reported by Paterson and Miller,[13a] requiring the stereoselective preparation of Me,*Si*,*Si* building block **V** (Figure 2).

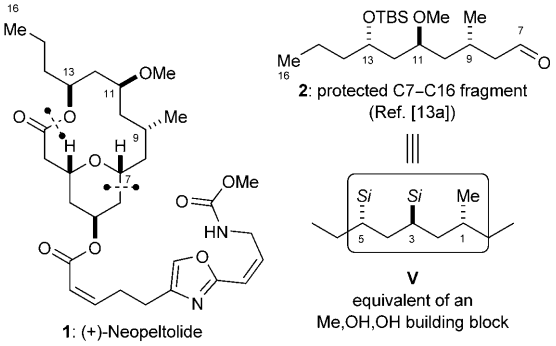

Figure 2. (+)-Neopeltolide (**1**) and its C7–C16 unit **2**.

A salient feature of the Feringa–Minnaard iterative syntheses is the exceptional catalyst control seen in each copper(I)-catalyzed 1,4-addition.[4] Our task at the outset was therefore to learn about the influence of the existing stereogenic carbon atom on stereoinduction in the possible stereochemical scenarios of Me,*Si* and *Si*,Me building block syntheses (Scheme 1).

- Scenario copper(I) catalysis (Scheme 1, upper): Our enantioselective rhodium(I)-catalyzed 1,4-addition yielded the *Si*-containing intermediate with perfect enantiomeric excess (**3**→**4**),[7b] and the α,β-unsaturated acceptor with *E* double-bond configuration[15] was accessed by a conventional three-step two-carbon homologation (**4**→**5**).[16a] The subsequent copper(I)-catalyzed conjugate methyl transfer with josiphos (racemic or either enantiomer) was not fully catalyst-controlled, with *anti* (matched case, **5**→*anti*-**6**) being preferred over *syn* relative configuration (mismatched case, **5**→*syn*-**6**).[17] The interfering substrate control might be attributed to the steric demand of the *Si* group.
- Scenario rhodium(I) catalysis (Scheme 1, lower): The methyl-group-containing precursor was prepared in high enantiomeric excess according to the Feringa–Minnaard methodology (**7**→**8**),[18] and the α,β-unsaturated acceptor with *Z* double-bond configuration[15] was again available through a straightforward three-step two-carbon homologation (**8**→**9**).[16b] The asymmetric rhodium(I)-catalyzed

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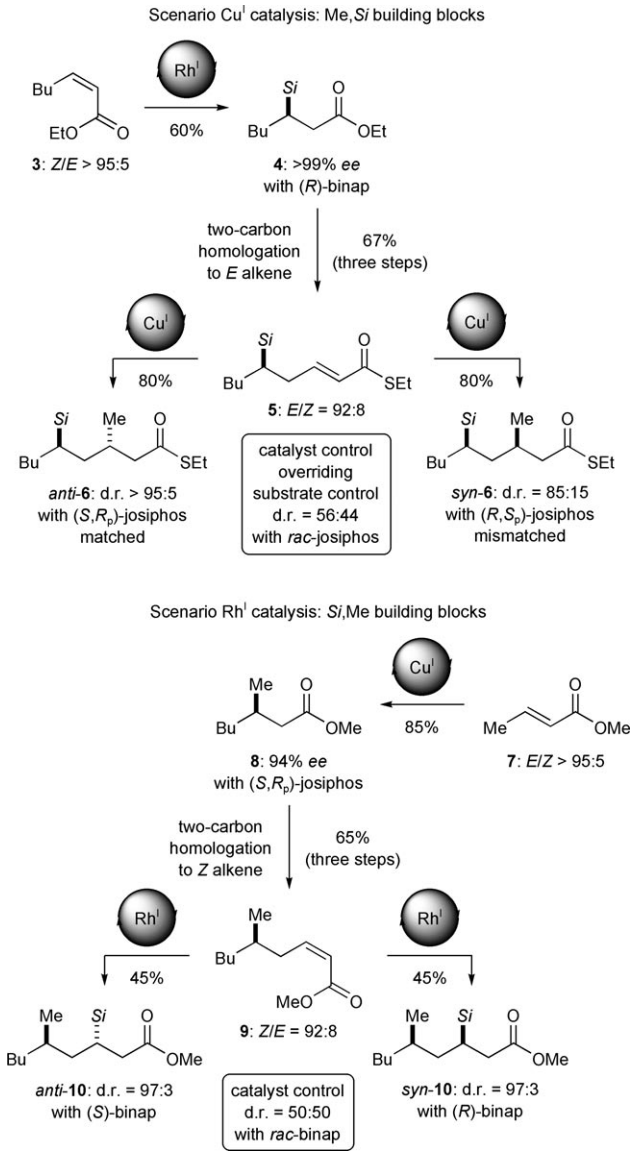
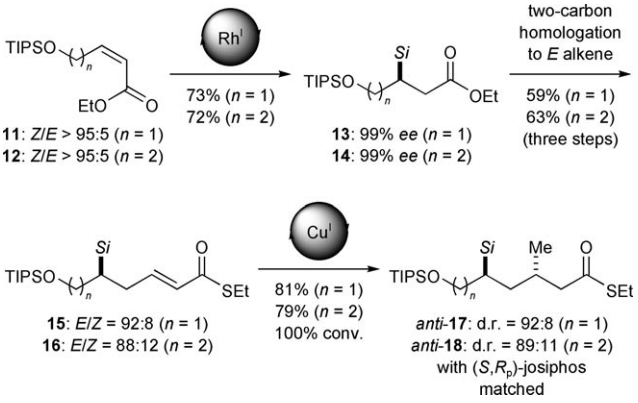


Scheme 1. Catalyst versus substrate control in the second iteration towards Me,*Si* and *Si*,Me building blocks. Rhodium(I)-catalyzed conjugate silyl transfer: $[Rh(cod)_2]OTf$ (5.0 mol%), binap (10 mol%), Me_2PhSi-Bpin[9] (2.5 equiv), Et_3N (1.0 equiv), 1,4-dioxane/H_2O 10:1, 45 °C; copper(I)-catalyzed conjugate methyl or butyl transfer: $CuBr{\cdot}SMe_2$ (5.0 mol%), josiphos (6.0 mol%), MeMgBr (1.2 equiv) or BuMgBr (1.4 equiv), *t*BuOMe, −78 °C; three-step homologations: a) DIBAL-H (3.5 equiv), THF, −78 °C; b) $(COCl)_2$ (1.5 equiv), DMSO (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, −78 °C; c) for *E* alkene[16a] $Ph_3P{=}CHC(O)SEt$ (1.4 equiv), $CHCl_3$, Δ or for *Z* alkene[16b] $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (1.4 equiv), KHMDS (1.4 equiv), [18]crown-6 (2.5 equiv), THF, −78 °C. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = cycloocta-1,5-diene, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethylsulfoxide, josiphos = 1-[2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphine, KHMDS = potassium hexamethyldisilazide, OTf = trifluoromethanesulfonate, pin = pinacolato, THF = tetrahydrofuran.

conjugate carbon–silicon bond formation then occurred with outstanding diastereocontrol in both cases (**9**→*anti*-**10** and **9**→*syn*-**10**).[19] The pronounced catalyst control agrees with the Feringa–Minnaard sequences in that no substrate control is imposed by the existing stereogenic tertiary carbon atom.

This survey shows that three out of four Me,*Si* and *Si*,Me combinations are accessible with excellent isomeric purity. It also reveals however that the silicon-bearing carbon atom is not innocent in the next iteration, and we found this to be true in the unselective preparation of the *Si*,*Si* array (not shown).

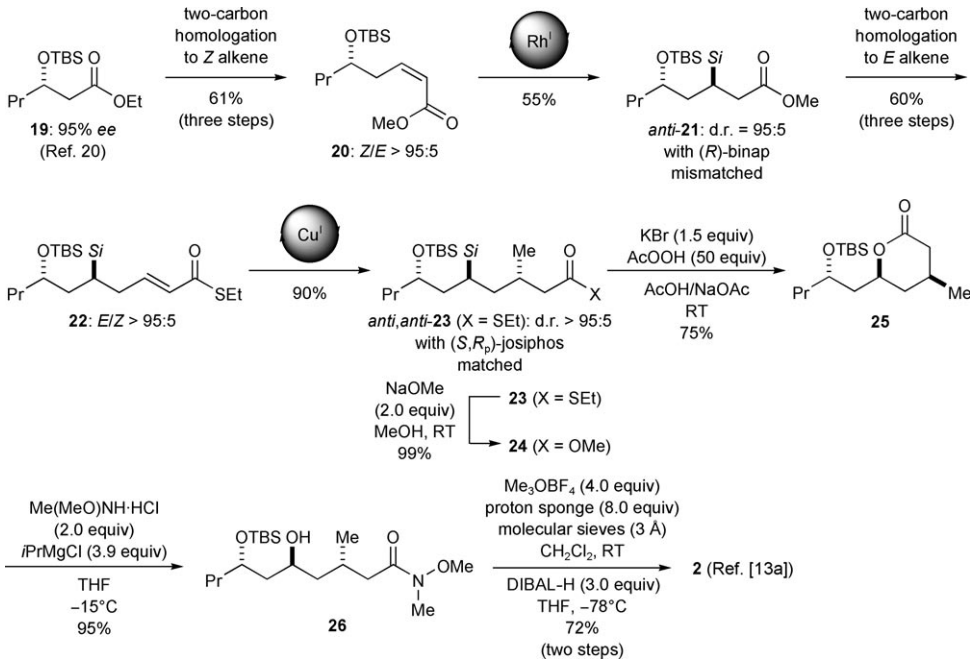
The problematic preparation of the *Si*,*Si* unit by consecutive silyl transfers brought about the issue of how to assemble the Me,*Si*,*Si* building block **V** required for the synthesis of **2** (Figure 2). This situation prompted us to test the role of an existing protected hydroxy group in α,β-unsaturated acceptors. Orthogonal protection of the hydroxy groups in **2** would also be secured. We were then delighted to see that γ- and δ-silyloxy-substituted compounds **11** and **12** performed well in the 1,4-addition (**11**→**13** and **12**→**14**, Scheme 2), exceeding any chemical yield previously obtained



Scheme 2. Conjugate silyl transfer onto γ- and δ-silyloxy-substituted α,β-unsaturated acceptors followed by conjugate methyl transfer (see Scheme 1 for reagents and reaction conditions).

for acyclic acceptors.[7b] Standard homologation (**13**→**15** and **14**→**16**) was followed by purely catalyst-controlled methyl transfer (matched cases; **15**→*anti*-**17** and **16**→*anti*-**18**). The *E*/*Z* ratios of **15** and **16** translate into the diastereomeric ratios of *anti*-**17** and *anti*-**18**, indicating that this time both double-bond isomers are reactive in the 1,4-addition (cf. **5**→*anti*-**6**; Scheme 1).[17]

With these results at hand, we turned to the synthesis of the C7–C16 fragment **2** (Figure 2 and Scheme 3). Chiral δ-silyloxy-substituted α,β-unsaturated carboxyl compound **20** was made available from the known protected β-hydroxy carboxyl compound **19**.[20] The choice of the hydroxy protecting group emerged as crucial, as its size (TES, TBS, or TIPS) had a marked influence on substrate control in the subsequent 1,4-addition. While TES was superior to TBS and TIPS in the conjugate addition, its lability in the later oxidative degradation of the carbon–silicon bond forced us to consider larger groups, such as TBS and TIPS. Only a few examples have been reported for the difficult Tamao–Fleming oxidation,[21] and control experiments verified that TBS protection is ideal. The conjugate addition using (*R*)-binap proceeded smoothly



Scheme 3. Synthesis of the C7–C16 fragment **2** of (+)-neopeltolide (**1**; see Scheme 1 for reagents and reaction conditions). TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl, proton sponge = 1,8-bis(dimethylamino)naphthalene.

to yield the desired *anti* diastereomer with good mismatched selectivity with d.r. = 95:5 (**20**→*anti*-**21**, Scheme 3). In the presence of (*S*)-binap, the matched isomer was formed with d.r. > 99:1 (**20**→*syn*-**21**; not shown). Homologation (*anti*-**21**→**22**) and *anti*-selective conjugate methylation (**22**→*anti*,*anti*-**23**) afforded the fully elaborated carbon framework as a single diastereomer. After thio-to-oxo transesterification (**23**→**24**), the Fleming procedure[10b,c] allowed selective oxidative degradation to form a lactone (**24**→**25**). Its opening to the Weinreb amide (**25**→**26**) was followed by methyl ether formation, and reduction to the carbonyl oxidation level completed the synthesis of the C7–C16 fragment (**26**→**2**).[22] The spectroscopic data were in accordance with those reported by Paterson and Miller.[13a]

Based on alternating conjugate silyl and methyl transfer, we accomplished a flexible iterative approach to the stereocontrolled synthesis of mixed methylated/hydroxylated linear carbon chains with methyl and hydroxy groups in 1,3-relationship. All diastereomers are accessible in principle. The 1,4-addition of nucleophilic silicon was found to be enhanced by an existing δ-silyloxy group, thus paving the way for the formal total synthesis of (+)-neopeltolide (**1**).

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