A Stereocontrolled Synthesis of Methyl (–)-Nonactate

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Abstract: A stereoselective synthesis of methyl (–)-nonactate is described. (*E*)-γ-Triethylsilyloxyalkene **13** generated from sulfone **10** and (*S*)-2-benzyloxypropanal underwent intramolecular iodoetherification in the presence of silver carbonate to provide *cis*-2,5-disubstituted tetrahydrofuran **8** as a key intermediate.

Key words: asymmetric synthesis, cyclizations, sulfones, nonactic acid, iodoetherifications

Nonactin **1** is a macrotetrolide ionophore antibiotic which has been isolated from a variety of *Streptomyces* cultures.[1] Nonactin is tightly bound to NH_4^+ and currently used in commercial ion selective electrodes (ISEs) for detecting the cation down to micromolar levels.[2] It consists of two molecules of (–)-nonactic acid (–)-**2** and two molecules of (+)-nonactic acid (+)-**2** arranged in an alternating order (Figure 1). The important structural feature of nonactic acid is the *cis*-2,5-disubstituted tetrahydrofuran, and in view of construction of that many syntheses of nonactic acids and its 8-*epi*-isomers in both optically active and racemic form have been reported.[3] But any completely sterocontrolled asymmetric cyclization using an electrophile has not been shown. Iodoetherification of γ-hydroxy-alkene[4] has been a useful method for the preparation of 2,5-disubstituted tetrahydrofuran and the Ag_2CO_3-mediated intramolecular iodoetherification of γ-triethylsilyloxyalkene was newly developed to accomplish the total synthesis of pamamycin-607.[5] In order to widen the scope of this method to another synthesis of natural product, we have investigated a stereocontrolled synthesis of methyl (–)-nonactate **15**. Herein we report our results.

For the synthesis of methyl (–)-nonactate **15**, the known alcohol **3** (62% de)[6] was silylated with chlorotriethylsilane to afford **4** which was separable from its diastereomer (Scheme 1). Olefin **4** was subjected to hydroboration and the resulting alcohol **5** was transformed into phosphonium salt **6** via the routine iodide formation. Wittig olefination of phosphonium salt **6** and (*S*)-2-benzyloxypropanal[7] was performed with *n*-BuLi in THF and HMPA to give (*Z*)-γ-triethylsilyloxyalkene **7**. For the preparation of *cis*-2,5-disubstituted tetrahydrofuran **8**, iodocyclization of **7** was carried out with iodine in the presence of silver carbonate in diethyl ether using the same method as reported.[5a] Disappointingly, only a 4:1 separable mixture of *cis*- and *trans*-tetrahydrofuran was gained at –20 °C and when toluene was used as a solvent the *cis*:*trans* ratio increased to 6.5:1. As a matter of course, to check the utility of this method, basic studies using bases such as sodium bicarbonate and potassium carbonate instead of silver carbonate were executed in various solvents and these induced decrease of reaction rate and stereoselectivity.

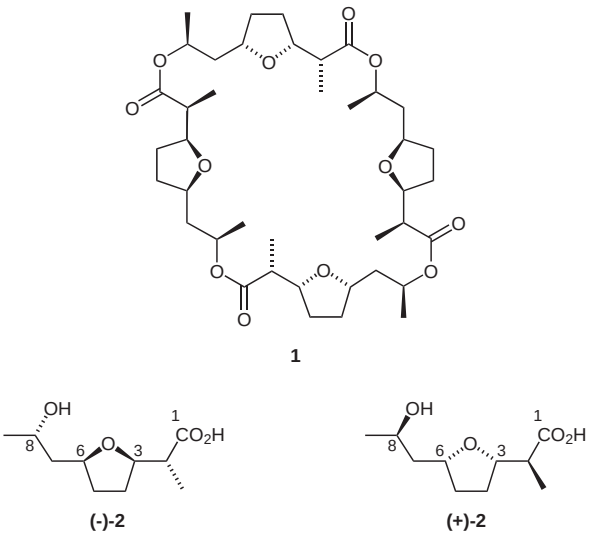

Figure 1 Nonactin and nonactic acids

As the stereochemical outcome of the cyclization of *cis*-olefin **7** fell short of our expectation, we now focused on the considerable influence of the olefin geometry on the cyclization stereochemistry.[4,8] So, isomerization of *cis*-olefin **7** was carried out using thiophenol and AIBN in toluene at 80 °C to give a 4:1 inseparable mixture of *trans*- and *cis*-olefins. Iodoetherification of this mixture was performed in the presence of silver carbonate and the *cis*:*trans* ratio increased up to 10:1.

Therefore, it was necessary that cyclization of pure *trans*-olefin **13** should be attempted, and sulfone olefination was executed (Scheme 2). Alcohol **5** was transformed into benzothiazole sulfone and 1-phenyl-1*H*-tetrazole sulfone via Mitsunobu reaction and oxidation, and the coupling reactions of each sulfone and (*S*)-2-benzyloxypropanal were performed.[9] But only 1:1 mixture of *trans*- and *cis*-olefins was gained. Accordingly, olefination using phenyl sulfone was carried out. The hydroxyl group of **5** was converted into sulfide using phenyl disulfide and tributylphosphine, and the subsequent oxidation with *m*-CPBA

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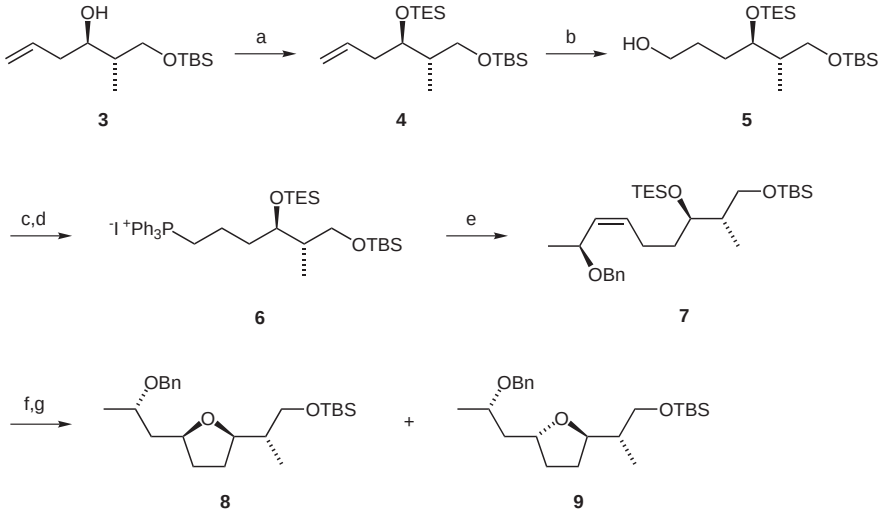
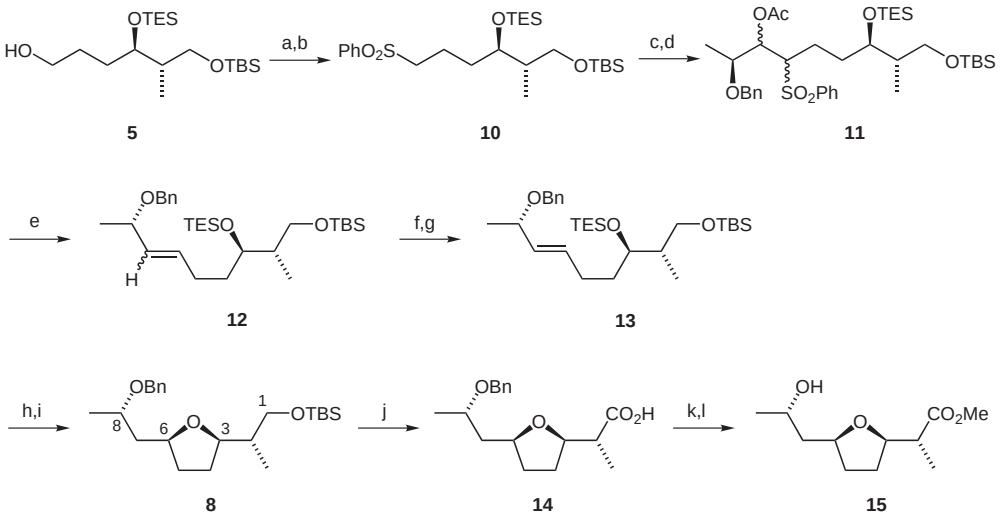


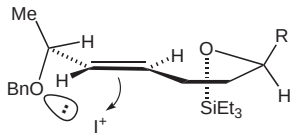
Scheme 1 *Reagents and conditions*: (a) TESCl, imidazole, CH_2Cl_2, r.t., 79% of desired diastereomer; (b) $H_3B{\cdot}SMe_2$, THF, r.t., then aq NaOH, H_2O_2, r.t., 81%; (c) PPh_3, I_2, imidazole, THF, r.t.; (d) PPh_3, K_2CO_3, CH_3CN, 90 °C, 92% (2 steps); (e) *n*-BuLi, THF, HMPA, –10 °C, then (*S*)-2-benzyloxypropanal, –78 °C to 0 °C, 68%; (f) I_2, Ag_2CO_3, PhMe, –20 °C; (g) Bu_3SnH, Et_3B, THF, r.t., 91% (2 steps).

gave sulfone **10** as the coupling partner of (*S*)-2-benzyloxypropanal. The coupling reaction was carried out using LDA and successive acetylation furnished β-acetoxysulfones **11**. Olefination of **11** using 5% sodium amalgam provided a 4.5:1 inseparable mixture of *trans*- and *cis*-alkenes **12**. Because the isomerization of *cis*-alkene **7** was not good on large scale, we selected this strategy for the preparation of the *trans*-alkene **13**. After detriethylsilylation of a mixture **12**, *trans*- and *cis*-γ-hydroxyalkene were separated and silylated to afford γ-triethylsilyloxyalkene. Iodoetherification of *trans*-alkene **13** was performed with iodine in the presence of silver carbonate in ether at –20 °C to give a mixture of *cis*-2,5-disubstituted tetrahydrofuran and its TBS deprotected product without any detectable *trans*-tetrahydrofuran. In case the reaction was carried out in toluene, only the desired *cis*-2,5-disubstituted tetrahydrofuran was obtained in 91% yield. Reductive deiodination of the cyclized product furnished **8**,[10] the stereochemistry of which was confirmed by the NOE experiments between H-3 and H-6 (4.0% enhancement from the *cis* relationship).

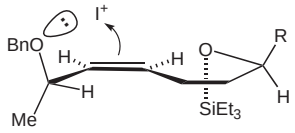
Then the reason why the olefin geometry affects the stereoselectivity can be explained as follows. The olefin can be attacked by I^+ on either face to give π complexes, which form reversibly. So, the diastereofacial selectivity of the process is dependent upon the relative abundances and reactivities of the complexes. It is thought that the conformational preference of both **16** and **17** to position



Scheme 2 *Reagents and conditions*: (a) $(PhS)_2$, Bu_3P, CH_2Cl_2, r.t., 92%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 83%; (c) LDA, THF, 0 °C, then (*S*)-2-benzyloxypropanal, 0 °C, 82%; (d) Ac_2O, DMAP, Et_3N, r.t., 88%; (e) 5% Na/Hg, NaH_2PO_4, MeOH, –20 °C, 82%; (f) PPTS, MeOH, 0 °C, 75% for *trans*-olefin; (g) TESCl, imidazole, CH_2Cl_2, r.t., 96%; (h) I_2, Ag_2CO_3, PhMe, –20 °C, 4 h, 91%; (i) Bu_3SnH, Et_3B, THF, r.t., 96%; (j) KF, Jones reagent, acetone, 0 °C, 91%; (k) $ClCO_2CH_3$, DMAP, Et_3N, CH_2Cl_2, 0 °C, 90%; (l) H_2, 10% Pd/C, MeOH, r.t., 94%.



16 *trans*, H in plane



17 *cis*, H in plane

Figure 2

the benzyloxy group as a directing group *syn* to I^+ arises because of stabilizing interaction between the positive charge and the oxygen lone pair electrons (Figure 2). On the basis of the Bartlett's theory, the steric bulk of the O-protecting group and its electrofugal properties are the main factors which induce the desired *cis*-1,3 stereorelationship via two transient *trans*-1,2 relationships.[4a] In the case of *cis*-olefin **17** the direction of attack by I^+ cause the formation of *trans*-tetrahydrofuran and this result does not correspond with the Bartlett's theory and the mixture was produced by equilibration. Next, TBS protected hydroxyl group of **8** was oxidized[11] using Jones reagent in the presence of potassium fluoride to give acid **14** which will be a key intermediate for a synthesis of nonactin via coupling with (+)-nonactic acid subunit. For the identification of **14**, it was esterified using methyl chloroformate and the resulting methyl ester was debenzylated with 10% palladium on charcoal under hydrogen atmosphere to furnish methyl (–)-nonactate **15** ($[\alpha]_D^{23} = -14.0$, $c = 1.20$, $CHCl_3$). Its spectral data were identical with those of the reported.[12]

In conclusion, a stereocontrolled synthesis of methyl (–)-nonactate **15** has been established using intramolecular iodoetherification of (*E*)-γ-triethylsilyloxyalkene in the presence of silver carbonate and it was shown that the geometry of olefin affected the stereoselectivity of iodoetherification greatly. Based on this result, further studies for a total synthesis of nonactin are now in progress in our laboratory.

Acknowledgement

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(10) Spectral data for **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (5 H, m), 4.59 (1 H, d, *J* = 11.6 Hz), 4.47 (1 H, d, *J* = 11.6 Hz), 4.05–3.95 (1 H, m), 3.78–3.72 (2 H, m), 3.70–3.63 (1 H, m), 3.48 (1 H, dd, *J* = 9.8 Hz, 6.9 Hz), 1.99–1.82 (2 H, m), 1.78–1.42 (5 H, m), 1.24 (3 H, d, *J* = 6.2 Hz), 0.89 (9 H, s), 0.88 (3 H, d, *J* = 6.8 Hz), 0.04 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 128.3, 127.7, 127.3, 80.5, 76.0, 73.1, 70.7, 65.7, 44.0, 41.3, 31.6, 28.6, 25.9, 20.4, 18.3, 13.1, –5.4; IR (neat) 1251, 1070, 1028, 1006, 834 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{40}O_5Si$: 392.2747, found: 392.2748; $[\alpha]_D^{23}$ = +23.0, *c* = 1.00, $CHCl_3$.

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