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STEREOCONTROLLED SYNTHESIS OF SEGMENTS FOR THE SYNTHESIS OF TYLONOLIDE BY USING A RELATIVE 1,2-ASYMMETRIC INDUCTION

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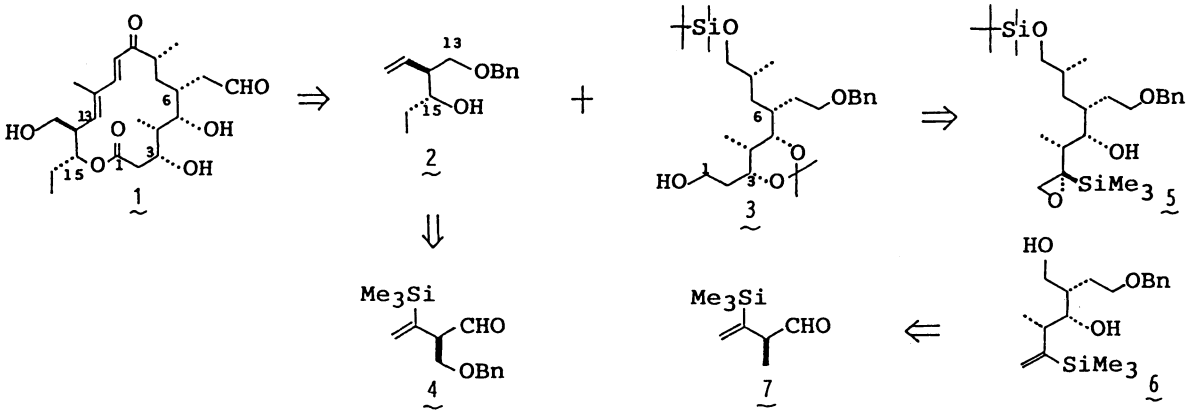
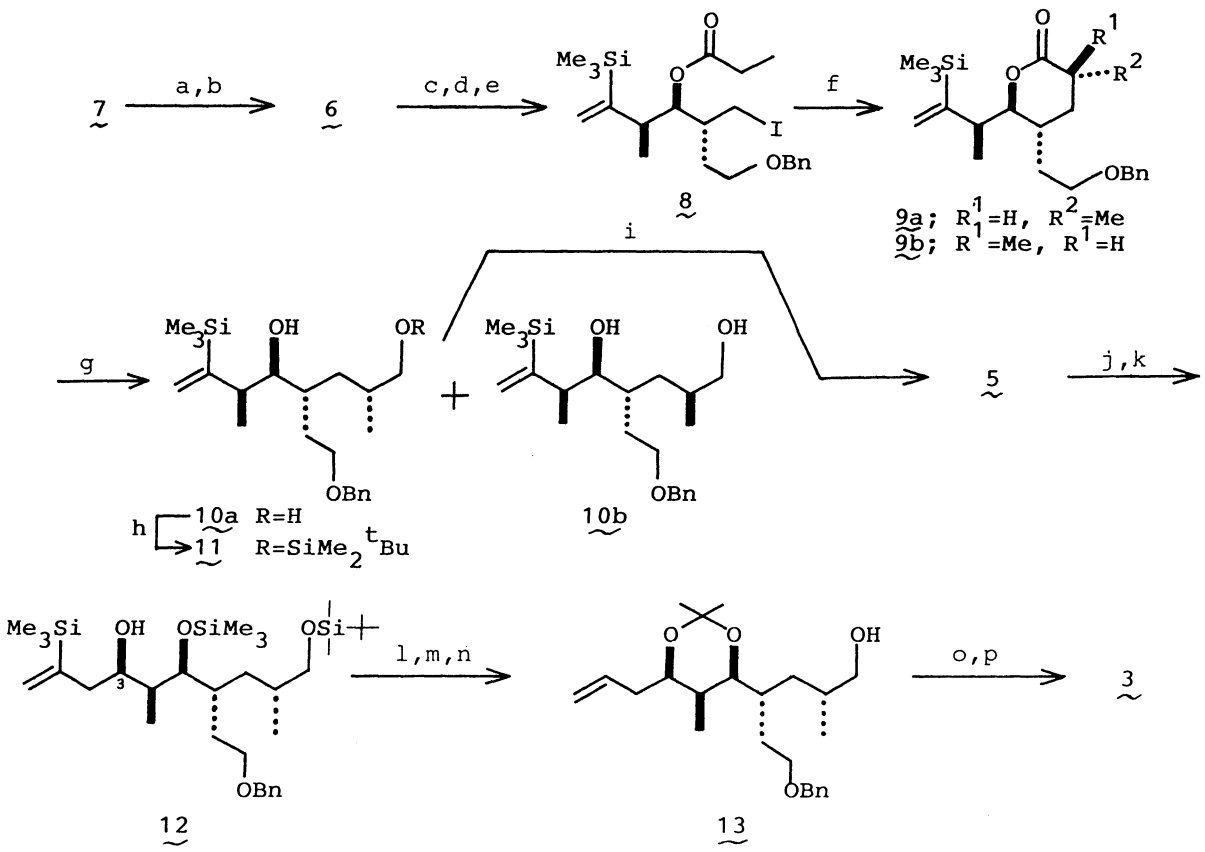
Two precursors corresponding to the C(1)-C(9) and C(13)-C(17) portions of tylonolide were synthesized in which all the chiral centers were induced correctly from the only one stereocenter existing in 2-methy-3-trimethylsilylbut-3-enal and 2-benzyloxymethyl-3-trimethylsilylbut-3-enal, respectively.

We have recently developed a new method for the stereocontrolled synthesis of optically active acyclic molecules which is based on a highly diastereoselective addition reaction of nucleophiles to α-alkyl-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds.[1] Using this method, we have synthesized some natural products such as blastmycinone,[2] serricornin,[3] corynomycolic acid,[4] and intermediates for the synthesis of erythronolide A[5] and 6-deoxyerythronolide B.[6] Herein we describe our effort to the synthesis of the aglycone of the medically important 16-membered ring macrolide antibiotic tylosin,[7] tylonolide (1), which has an unique structural and stereochemical feature absent in the macrolide selected earlier as our synthetic targets.[5,6] A retrosynthetic analysis of 1 similar to those applied earlier[8] dissects 1 into three fragments: the left-hand [C(13)-C(17)] 2, olefinic part [C(10)-C(12)], and the right-hand [C(1)- C(9)] 3. We considered the aldehydes 4 and 7[1c] as starting compounds for the synthesis of 2 and 3, respectively (Scheme 1).

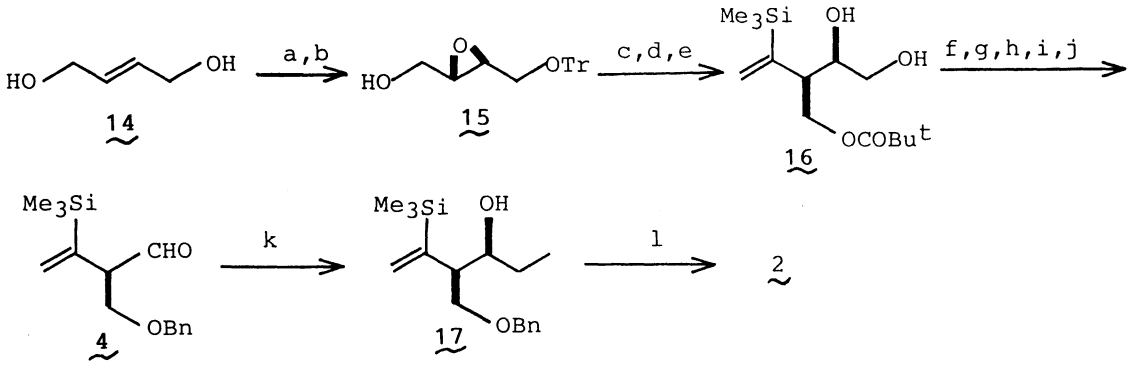


Scheme 1.



Scheme 2.

(a) $BnOCH_2CH_2CH_2CO_2BHT$, LDA; (b) $LiAlH_4$; (c) TsCl, C_5H_5N; (d) KI; (e) EtCOCl; (f) $KN(SiMe_3)$; (g) $LiAlH_4$; (h) $^tBuMe_2SiCl$; (i) TBHP, $VO(acac)_2$; (j) ^tBuOK; (k) $CH_2=C(SiMe_3)MgBr$, CuI; (l) $^nBu_4NF$; (m) NaH, HMPA; (n) $Me_2C(OMe)_2$, pTsOH; (o) $^tBuMe_2SiCl$; (p) O_3, MeOH, Me_2S then $LiAlH_4$



Scheme 3.

(a) TrCl, Et_3N; (b) TBHP, $VO(acac)_2$; (c) $CH_2=C(SiMe_3)MgBr$, CuI; (d) ^tBuCOCl; (e) Cl_2CHCO_2H; (f) $Me_2C(OMe)_2$, PPTS; (g) $LiAlH_4$; (h) $PhCH_2Br$, NaH; (i) HCl; (j) $NaIO_4$; (k) EtMgBr, Et_2O, -78°C; (l) NaH, HMPA.

Synthesis of the right-hand fragment 3 (Scheme 2): Addition of the lithium enolate derived from BHT ester of 4-benzyloxybutanoic acid to the aldehyde 7 (>95% ee) proceeded diastereoselectively as in the case of BHT ester of propionic acid[1d] to give the aldol which upon reduction with $LiAlH_4$ afforded the diol 6 ($[\alpha]_D^{25}$ -4.86° (c 1.44, $CHCl_3$)) as the sole product (81%). The diol 6 was transformed into 8 ($[\alpha]_D^{25}$ +8.87° (c 1.08, $CHCl_3$)) by tosylation, displacement with KI, and esterification with propionyl chloride in 57% yield. Intramolecular alkylation with $KN(TMS)_2$ provided a mixture of the lactones 9a and 9b in 76% yield. Without separation, the mixture of the lactones was reduced with $LiAlH_4$ to give rise to 10a (37%) and the corresponding epimeric diol 10b (58%), which could be easily separated by gravity column chromatography on silica gel: 10a, R_f = 0.77; 10b, R_f = 0.43 (1 : 1, hexane-Et_2O).[9] The undesired isomer 10b was transformed to a 1 : 1 mixture of the diols 10a and 10b by a three-step sequence of lactonization, epimerization, and reduction (71% yield), thus 10b could be recycled to the desired compound 10a. The remaining chiral center at C(3) of 3 was introduced selectively as follows. Epoxidation (TBHP, $VO(acac)_2$) of the alcohol 11 derived from 10a by selective protection proceeded diastereoselectively to afford 5 (96%) as the sole product.[6] Treatment of 5 with t-BuOK caused the 1,4-$SiMe_3$ group shift to give the corresonding silyl ether,[2,6] which on reaction with 1-trimethylsilylvinylmagnesium bromide led to 12. The transformation of 12 into 13 ($[\alpha]_D^{25}$ +13.4° (c 1.21, $CHCl_3$)) was achieved in a straightforward fashion. The total yield of 13 from 5 was 60%. Finally, conversion of 13 into the silyl ether followed by ozonolysis and subsequent reduction afforded 3 ($[\alpha]_D^{25}$ +6.16° (c 0.55, $CHCl_3$)) in 65% yield.[10]

Synthesis of the left-hand fragment 2 (Scheme 3): The required aldehyde 4 was synthesized as follows. Monotritylation of 14 followed by epoxidation (TBHP, $VO(acac)_2$) gave 15 (43%). Epoxide ring opening reaction of 15 with 1-trimethylsilylvinylmagnesium bromide[1c] followed by esterification with pivaloyl chloride and deprotection gave 16, from which 4 was prepared in a straightforward fashion in good yield. Reaction of EtMgBr with 4 proceeded stereoselectively to give the syn alcohol 17 in 87% yield.[1a] No anti isomer was detected. Finally protodesilylation[11] of 17 using NaH in HMPA furnished 2 (69%).

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References

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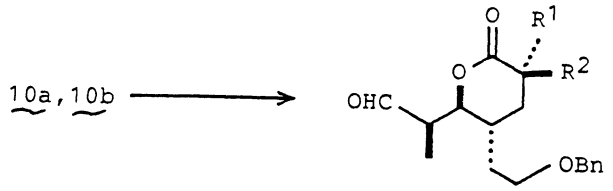
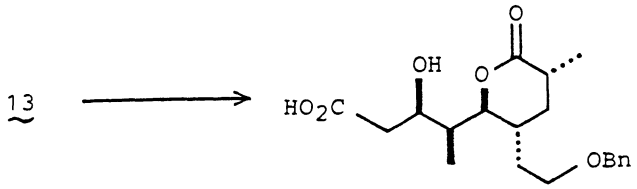
9) Both epimers 10a and 10b were transformed into the lactones i and ii, respectively, via a three-step sequence [(1) KH, HMPA; (2) Ag_2CO_3, Celite; (3) O_3, MeOH then SMe_2]. ^1H NMR spectrum of i is identical with that reported by Masamune.[8c)]



i, R^1=Me, R^2=H
ii, R^2=H, R^2=Me

10) The stereochemistry of 3 was confirmed by transformation of 13 into the known compound iii[8c)] by oxidation (PDC, DMF) followed by ozonolysis (O_3, MeOH then H_2O_2, HCOOH).



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