Allylsilane in Synthesis: New Syntheses of (±)-Desepoxy-4,5-didehydromethylenomycin A and (±)-Xanthocidin

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(±)-Desepoxy-4,5-didehydromethylenomycin A and (±)-xanthocidin were synthesised *via* a common β-silyl enone intermediate obtained from an efficient, highly regioselective oxidation of an allylsilane.

The γ-site selectivity of electrophilic attack on allylsilanes[1] or α-silyl-substituted allyl anions[2] is well known and has found numerous synthetic applications. In contrast, regioselectivity in the reactions of α-silyl allyl radicals or cations (Figure 1) has only received scant attention[3,4] and its synthetic potential has not been exploited. In this communication, we report a new, general route to the synthesis of several structurally related cyclopentanoid antibiotics,[5] as exemplified by desepoxy-4,5-didehydromethylenomycin A (**1**) and xanthocidin (**2**), in which regiocontrol is crucial.

As shown in Scheme 1, our synthesis started with a readily available allylsilane (**3a**).[6] Catalytic monodechlorination with tri-n-butylstannane[7] followed by silver ion-assisted cyclisation, converted it into lactone (**5a**),† which has been used to synthesise sarkomycin,[8] the parent member of cyclopentanoid antibiotic family. With the carboxy and *exo*-methylene groups in their protected forms, we discovered an efficient way to elaborate the cyclopentene ring of (**5a**) to give directly a single enone (**6**) in up to 70% yield. The method consists of heating (**5a**) with a three-fold excess of t-butyl hydroperoxide (*ca.* 80% solution in CH_2Cl_2 or Bu^tOH) in the presence of 10 mol% of a copper(I) salt (preferably chloride), with small portions of fresh oxidant added at 2 h intervals until the

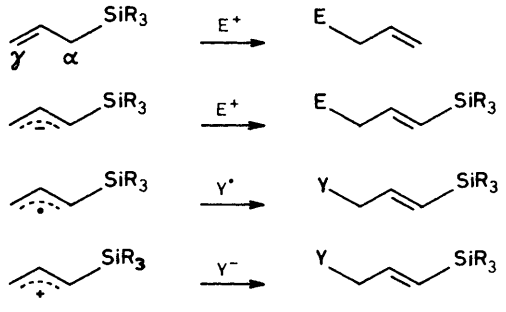
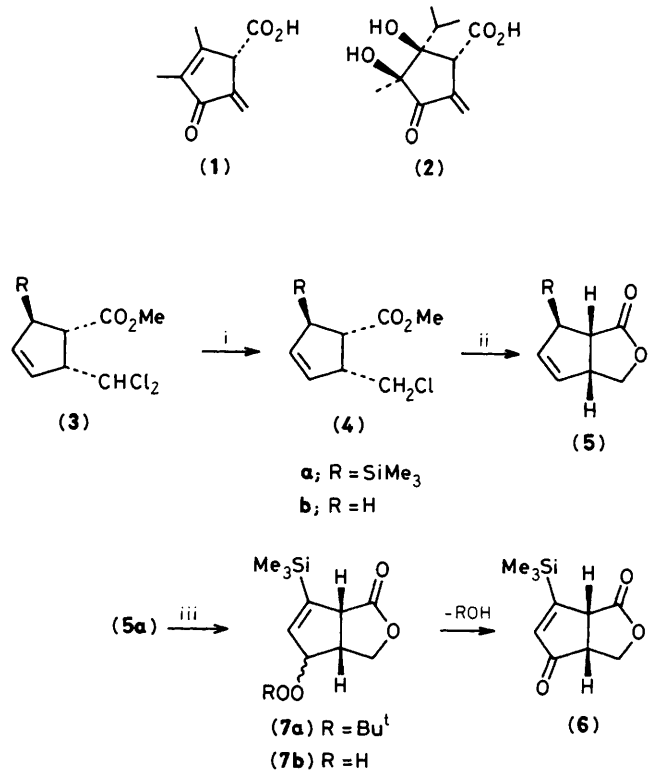
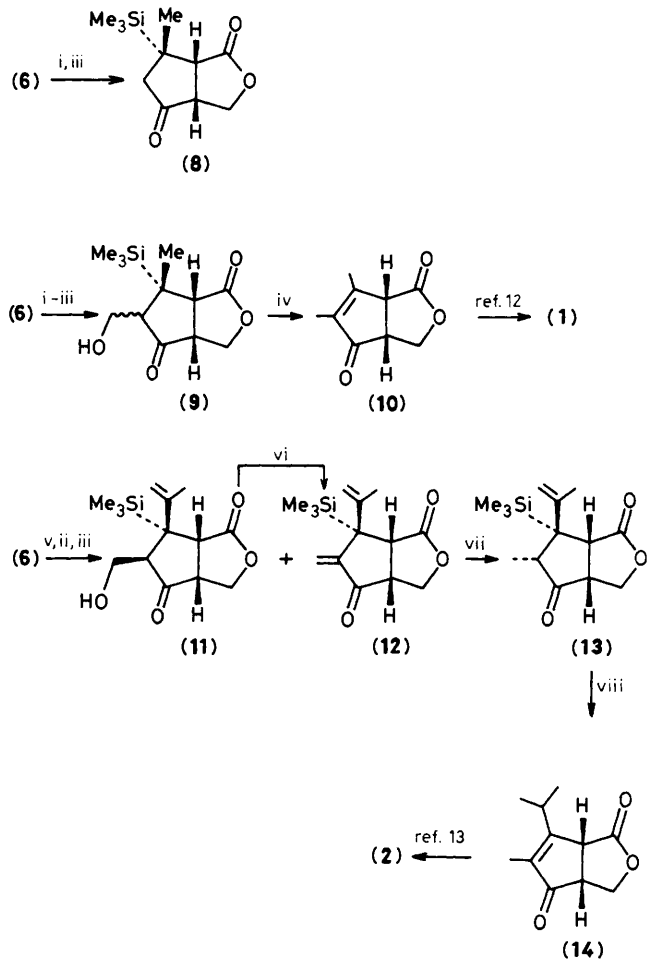


Figure 1

† Satisfactory elemental (C, H) and spectral (i.r., u.v., n.m.r., mass) analyses were obtained for all new compounds.



Scheme 1. *Reagents:* i, $NaBH_4$, 0.1 equiv. Bu^n_3SnCl, catalytic amount of azoisobutyronitrile, EtOH, *hv*, room temp., 40 h (90%); ii, $AgNO_3$, H_2O, dioxane, 60 °C, 9 h (64%); iii, Bu^tOOH, 10% CuCl, 55 °C, 10 h, (2—5 mmol scale, 67—70%).



Scheme 2. *Reagents:* i, Me_2CuLi, Et_2O, $-10\rightarrow0$ °C, 4 h; ii, anhydrous CH_2O, $-40\rightarrow-20$ °C, 10 min; iii, aq. NH_4Cl; iv, TsOH, PhH, reflux, 3 h; v, 2 equiv. $(CH_2{=}CMe)Li$, CuCN, Et_2O, −70 °C, 3 h; −40 °C, 13 h; vi, TsCl, pyridine, room temp., 36 h; vii, 1 equiv. H_2, Pd–C, EtOH, 5—10 °C; viii, TsOH, Et_2O, reflux, 36 h. Ts = *p*-Me-C_6H_4-SO_2.

reaction is complete. Without catalysis by the copper(I) salt, a higher temperature and a longer reaction time were required, with a lower yield of (**6**), (30—50%) and its purification was much less convenient.

This reaction is thought to proceed *via* a free radical type mechanism;[9] two peroxide intermediates, (**7a**) and (**7b**), could be isolated when the reaction was interrupted before the appearance of (**6**). To show that the trimethylsilyl group is responsible for the observed regioselectivity, we also attempted the oxidation of (**5b**) under identical conditions. As expected, a low degree of conversion and a 1 : 1 mixture of two isomeric enones were obtained.[10] It should also be noted that attempts to oxidise (**5a**) using oxygen and Wilkinson's catalyst failed; (**5a**) was found to be surprisingly stable under conditions where 3-trimethylsilylcyclopentene would be rapidly oxidised.[4] This is understandable since the bulky rhodium catalyst would be required to co-ordinate from the more hindered *endo* side of (**5a**). Thus, our method using the copper(I) catalyst has the advantage of being much less sensitive to the steric environment.

In the second stage of the synthesis, appropriate alkyl substituents for the different target molecules were introduced onto (**6**) by a one-pot, tandem alkylation procedure (Scheme 2). Conjugate addition of dimethylcuprate[11] onto (**6**) went smoothly to give a crystalline product (**8**), with the trimethylsilyl group in an *endo* position, as established by a nuclear Overhauser effect n.m.r. experiment. To synthesise (**1**), the enolate intermediate in the conjugate addition was trapped with anhydrous formaldehyde to produce (**9**) as a mixture of diastereoisomers in an overall yield of 57%. Upon mild acid treatment, (**9**) was dehydrated and then protodesilylated to give (**10**) in 80% yield. This compound could be converted into (**1**) by a known procedure.[12]

For (**2**) the conversion is less straightforward. Since attempts with isopropylcopper(I) reagents failed, isopropenylcopper(I) has to be used instead for successful conjugate addition to (**6**). After hydroxymethylation with formaldehyde, a crystalline dienone (**12**) was obtained along with the expected alcohol in a 1 : 1 ratio and a total yield of 66%. This dienone was apparently derived from the less stable epimer of (**11**), since (**11**) was found to be stable and had to be transformed into (**12**) by a tosylation–elimination sequence. In practice the separation of (**11**) and (**12**) was unnecessary and the yield of (**12**) from (**6**) in four steps was 55%. The partial hydrogenation of (**12**) presented no additional difficulty: the crystalline compound (**13**) was obtained as the sole product in 89% yield. After acid treatment, it gave directly a 76% yield of the protodesilylated and rearranged product (**14**), whose conversion into (**2**) has also been documented.[13]

In comparison with existing syntheses,[12,13] our route has two distinctly favourable features: (i) an oxidation step with regiocontrol and thus a better yield,[14] and (ii) introduction of substituents onto a common intermediate at a late stage,

which should allow easy adaptation for the preparation of analogues.

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