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Synthesis of (+)-didesmethylmethylenomycin A methyl ester

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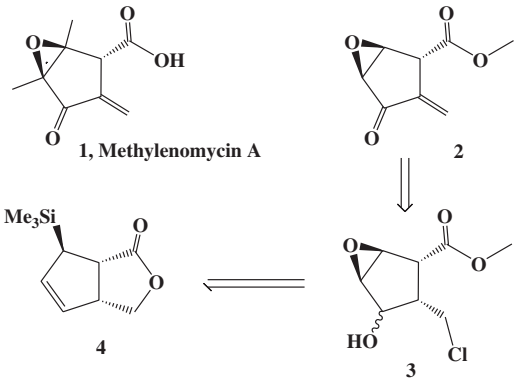
ABSTRACT

A concise and efficient synthesis of the new compound—(+)-didesmethylmethylenomycin A methyl ester from chiral building block **4** has been achieved.

1. Introduction

Cyclopentenone antibiotic methylenomycin A **1**, isolated from the *Streptomyces* bacteria, attracted attention as a highly functionalized structure with several electrophilic centers. Methylenomycin A is active against gram-positive and gram-negative bacteria as well as effective against Lewis lung carcinoma of mice.[1,2] Biological activity of conjugated structures like **1** is known to be associated with their ability to the form covalent bonds with SH- and NH_2-groups of biotarget proteins.[3,4] It appears for us that two vicinal Me-group in the structure of methylenomycin A diminish significantly electrophilic properties of the oxirane fragment of the molecule. In the search for the more active analogues we have decided to synthesize the sterically less hindered didesmethyl analogue **2**. Moreover, in contrast to methylenomycin A, the (+)-I-effect of two Me-groups, which decreases acceptor properties of *exo*-methylene electrophilic center is excluded in **2** (Scheme 1).



Scheme 1. Retrosynthetic analysis for **2**.

2. Results and discussion

In the synthesis of **2** the previously obtained lactone **4**[5] was selected as the chiral source. The latter is a retron of compound **3**, which in turn is a close precursor of **2**. On the way to **3** opening of the lactone ring was carried out by the action of $SOCl_2$ in methanol. This reaction proceeds smoothly at rt with formation of the chloroester **5** in 89% yield. The epoxidation of **5** with 1.1 equiv of *m*-CPBA resulted in a rapid formation of a mixture of unstable epoxides **6**+**7** (~1 h, monitoring by TLC), from which the α-epoxide **6** (major isomer with *anti* orientation of epoxide cycle relative to TMS-group)[6] transformed smoothly for 12 h into allylic alcohol **8**. In contrast to **6**, β-epoxide **7** was less active at this transformation and its complete conversion was achieved only for 72 h. Fragmentation of epoxides **6** and **7** was achieved by acidic conditions (1 N H_2SO_4/dioxane or 1 N H_2SO_4/THF) at rt for 3 h, but the yield of the mixture of allylic alcohols **8**+**9** was significantly

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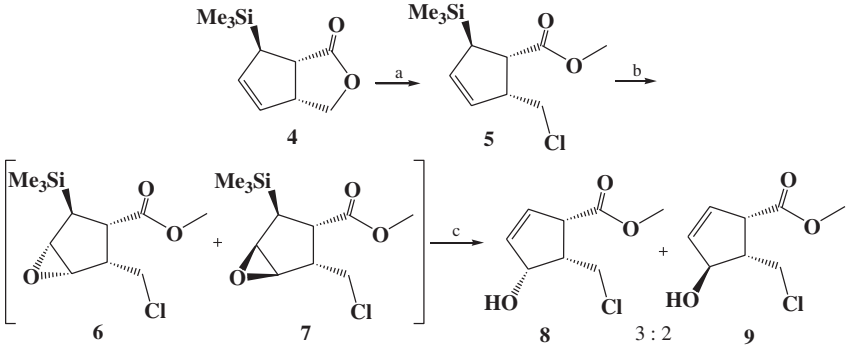
decreased due the formation of by-products. The best result was obtained when carrying out the epoxidation in the presence of catalytic amounts of PPTS. In this case the completed transformation of mixture **6**+**7** into compounds **8** and **9** in the ratio 3:2 was performed for 8 h without formation of by-products (Scheme 2). Epimers **8** and **9** were easily separated by column chromatography on SiO_2.

3. Conclusion

We have developed a convenient route to enantiomerically pure (+)-didesmethylmethylenomycin A methyl ester from a readily available starting compound **4**. The key steps of the approach: (a) easy cleavage of lactone cycle **4** by treatment with methanolic HCl; (b) preparation of the allylic α,β-hydroxycyclopentenes **8** and **9** by the treatment of **5** with *m*-CPBA in the presence of catalytic amounts of PPTS; (c) stereoconvergent transformation of the latters by re-epoxidation into β-epoxides **10** and **11**; (d) and finally, the oxidation of **10** and **11** by treatment with PCC led to analogue of methylenomycin A **2**.



a) $SOCl_2$-MeOH (1:5), rt, 7 h, 89%; b) 1.1 eq. *m*-CPBA, CH_2Cl_2, 0 °C to rt, 1 h; c) PPTS, 8 h, rt, 94%.

Scheme 2. Preparation of allylic alcohols **8** and **9**.

Configuration of the hydroxyl group of the allylic alcohols **8** and **9** was deduced from the chemical shifts of the proton at C2. Due to the steric compression in **8** its value upfield compared to **9** (Fig. 1).[7] Moreover, the chemical shifts of C2 and C3 signals in the ^{13}C NMR spectrum in case of α-epimer **8** also are upfield (possibly due to the steric *syn*-interaction of substituents). The observed NOE between H at C3 (δ 4.53 ppm) and H at C2 (δ 2.60 ppm) in **8** also confirms their cis orientation.

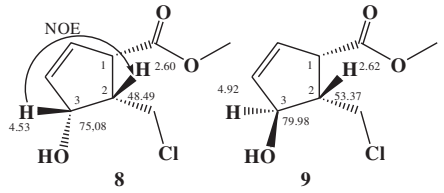


Fig. 1. Structures of the allylic alcohols **8** and **9**.

At the next step re-epoxidation of the individual allylic alcohols **8** and **9** with *m*-CPBA proceeded stereospecifically leading to epoxyalcohols **10** and **11**, respectively, each with β-configuration of epoxide ring. The extremely high selectivity of formation of **10** may be explained as a result of steric control of the *m*-CPBA attack from β-side of **8**. The directing effect of the hydroxyl group[8] in **9** promotes the formation of **11**. The observed NOE between H at C4 (δ 4.27 ppm) and both protons of epoxide ring (δ 3.64 ppm) in **11** also confirms their cis orientation. The absence of the coordination control in **10** could be explained by a possible intramolecular {–O–H···Cl– or –O–H···O=C–}-binding. The epoxyalcohols **10** and **11** were oxidized by treatment with PCC in CH_2Cl_2, leading to the analogue of methylenomycin A **2** in 85 and 93% yield, respectively (Scheme 3). It should be noted that **10** was oxidized significantly slower compared to **11** (possibly due to the steric interaction).

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried out in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 precoated foil plates. Column chromatography was conducted using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line at 589 nm on a Perkin–Elmer, Model 241 MC polarimeter at 20 °C. IR (infrared spectra) were recorded on a Shimadzu IRPrestige-21 spectrometer as Nujol mull or as neat thin films on KBr plates (film) and were reported in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^1H and 75.47 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Chemical shifts are reported in δ unit-parts per million (ppm) downfield from tetramethyl silane (TMS) as the internal reference. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet, t, triplet; q, quartet; quint., quintet. Mass spectra were recorded on Shimadzu LCMS QP-2010EV (APCI) spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.

4.2. Synthesis of methyl (1*S*,2*R*,5*R*)-5-chloromethyl-2-(trimethylsilyl)cyclopent-3-ene-1-carboxylate 5

To a stirred solution of (0.20 g, 1.0 mmol) **4** in methanol (5 mL) at 0 °C was added dropwise a solution of thionyl chloride (3 mL) in methanol (10 mL). The reaction was monitored by TLC (1:5 ethyl acetate/petroleum ether) and after stirring for 7 h at