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SYNTHESIS OF DEEPOXY-4,5-DIDEHYDROMETHYLENOMYCIN A AND METHYLENOMYCIN A METHYL ESTERS

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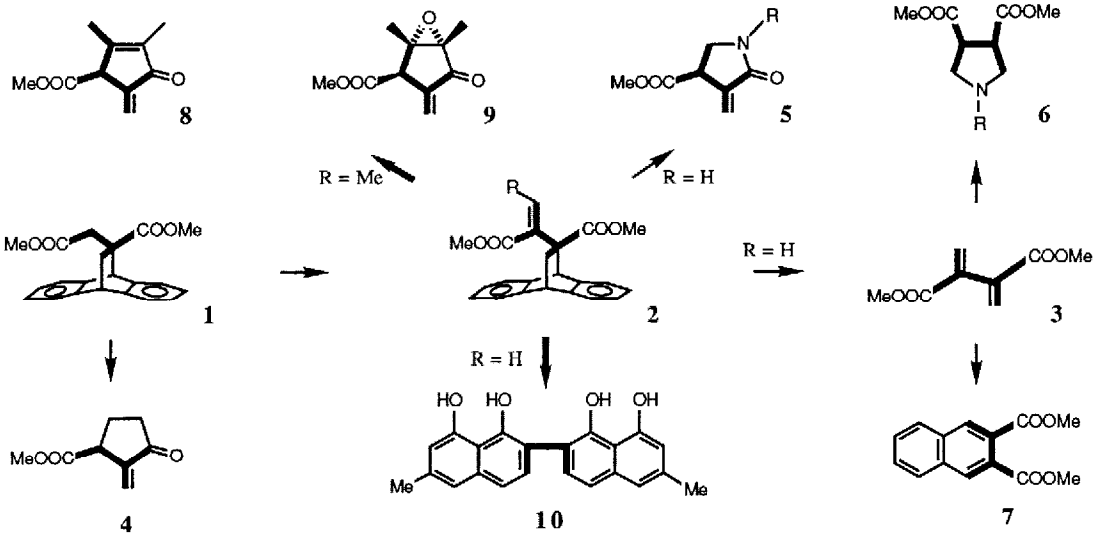
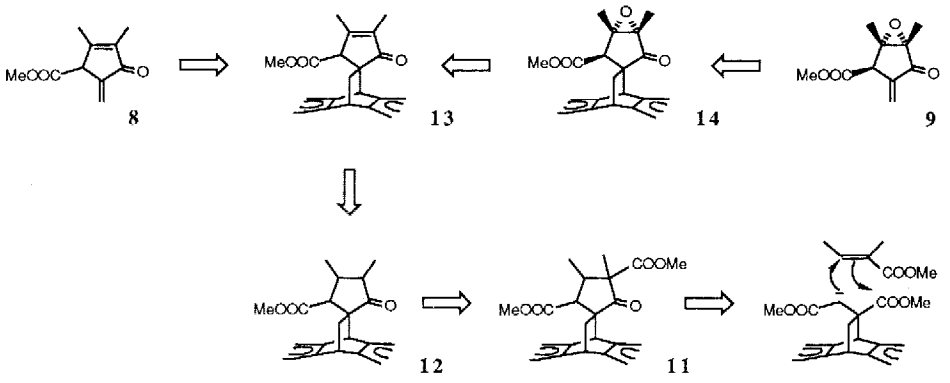
Abstract : [±]-Deepoxy-4,5-didehydromethylenomycin A methyl ester **8** and [±]-methylenomycin A methyl ester **9** are synthesized from anthracene adduct **2** via a common intermediate **13** . Flash vacuum pyrolysis of adduct **13** gives **8** , while stereospecific epoxidation of **13** followed by pyrolysis yields **9** .

The versatile use of anthracene adducts as building blocks in organic synthesis has been demonstrated in the construction of various natural products, [1] for example, the use of itaconate-anthracene adduct **1** in the synthesis [2] of sarkomycin **4** , and the use of **2** and **3** , both derived from **1** , in the syntheses of aza-sarkomycin **5** , [3] pyrrolidine **6** and naphthalene derivative **7** .[4] In this and the accompanying letter we report other modes of assemblage with anthracene adducts as illustrated by the syntheses of cyclopentenoid antibiotics, **deepoxy-4,5-didehydromethylenomycin A** and **methylenomycin A** methyl esters, **8** and **9** , [5,6] and the anthelmintic drug, **diospyrol 10** . [7]



The syntheses of **8** and **9** are planned through a common intermediate **13** which is potentially convertible either to **8** by direct flash vacuum pyrolysis, or to **14** via stereospecific epoxidation prior to pyrolysis. In principle, **11**, the precursor of **13**, should be obtainable via tandem Michael addition-Dieckmann condensation [2] between methyl tiglate and the ester enolate derived from **1**, as shown in **Scheme I**. Thereafter, the conversion of **11** to **13** should be straightforward.

Scheme I



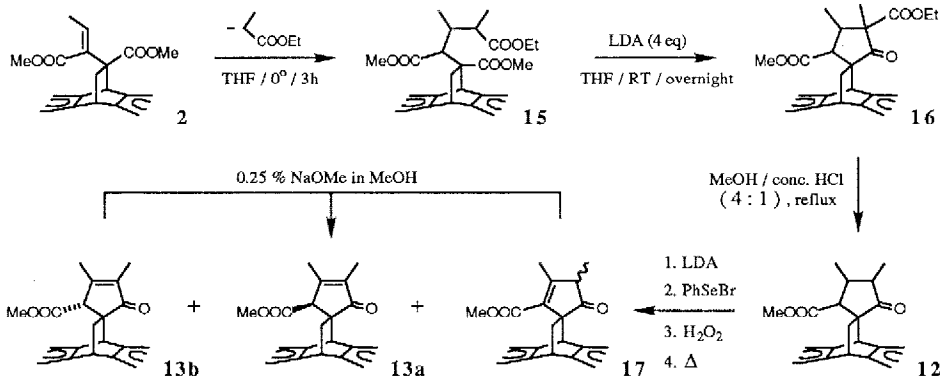
However, unlike previous results, [2] treatment of the enolate from **1** with methyl tiglate under various reaction conditions resulted in the recovery of a large amount of starting material **1** together with traces of unidentified products. Michael addition reaction must be proceeding here at a much slower rate than proton exchange to yield **1** and the corresponding tiglate-derived enolate. [8] We therefore decided to modify the approach, starting, instead, from adduct **2** [R = Me], prepared by ethylenation of **1** via Stobbe condensation. [9]

Michael addition of ethyl propionate anion to **2** readily takes place at 0^{0} in THF solution, giving **15** as a mixture of stereoisomers as indicated by nmr. Without separating the isomers the crude reaction mixture is filtered through a short silica gel column [dichloromethane], then further treated with excess LDA [4 equivalents] in THF at room temperature and left to stir overnight to effect a clean conversion of **15** to **16** via a Dieckmann condensation reaction. The remarkable ease with which tertiary ester **16** can be hydrolysed and subsequently decarboxylated under acidic conditions[2] is quite noteworthy. Thus, refluxing in methanol / conc. hydrochloric acid [4 : 1], diester **16** yields **12** as a colourless semi-solid. TLC analysis [silica gel ; dichloromethane /hexane = 1 : 1 as eluant] of crude **12** reveals two major isomers which, if desired, can be separated. However, we find it more convenient to directly subject the crude mixture **12** to the next reaction.

Conversion of **12** to the key intermediate **13** via selenoxide elimination follows standard procedures, [10] the reaction giving **13a** , **13b** , and a single isomer of **17** in 38 % , 11 % and 1.5 % isolated yields respectively [silica gel ; dichloromethane / hexane = 1 : 1] as calculated from starting material **2**. Stereochemical assignment of **13a** and **13b** is made according to their nmr spectra in which the carbomethoxy group of **13b** appears at δ 3.57 while that of**13a** resonates at a higher field [δ 3.37] due to anisotropy effect of the aromatic nucleus. [2] A subsequent observation that enones **13b** and **17** quantitatively convert to the thermodynamically more stable isomer **13a** in methanolic sodium methoxide solution at room temperature allows equilibration of the selenoxide elimination reaction products. Thus, by leaving the mixture of

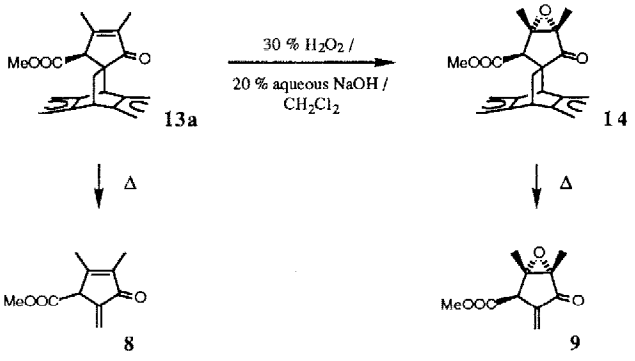
enones to stir in 0.25 % methanolic sodium methoxide, **13a** is obtained as the sole product in 53 % yield from **2** **[Scheme II]**.

Scheme II



In the final step of the synthesis of deepoxy-4,5-didehydromethylenomycin A methyl ester **8**, flash vacuum pyrolysis of **13a** at 450 ° / 0.01 mm gives, nearly quantitatively, pure [±]-**8**. [11]

The second synthesis, that of methylenomycin A methyl ester **9**, requires stereospecific epoxidation of **13a**. The requisite stereochemistry of epoxide ring in **9** being *trans-* to the carbomethoxy group, it is serendipitous that**13a** is the thermodynamically most stable isomer, because the steric combination present in **13a** [both carbomethoxy group and methylene bridge of the anthracene adduct on the same side] should strongly direct epoxidation to the opposite, less hindered side. True to anticipation, alkaline-hydrogen peroxide treatment of **13a** gives only one product, the methylenomycin A methyl ester-anthracene adduct **14** [71%], whose stereochemical integrity is confirmed by X-ray analysis. [12]



Finally, standard flash vacuum pyrolysis of **14** gives methylenomycin A methyl ester, [±]-**9**,[11] and thus completes our synthesis.

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11. All compounds described are properly characterized. Elemental analyses were performed by Scientific and Technological Research Equipment Center, Chulalongkorn University, Bangkok.
12. X-ray analysis of compound **14** was performed by Dr. N. Chaichit of Silpakorn University, Thailand and Dr. B. Skelton of the University of Western Australia.

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