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A GENERAL AND EFFICIENT STRATEGY FOR DETERMINING THE STEREOSTRUCTURE OF 1,3-POLYOL

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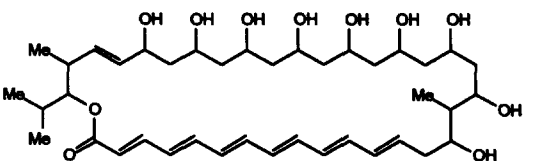
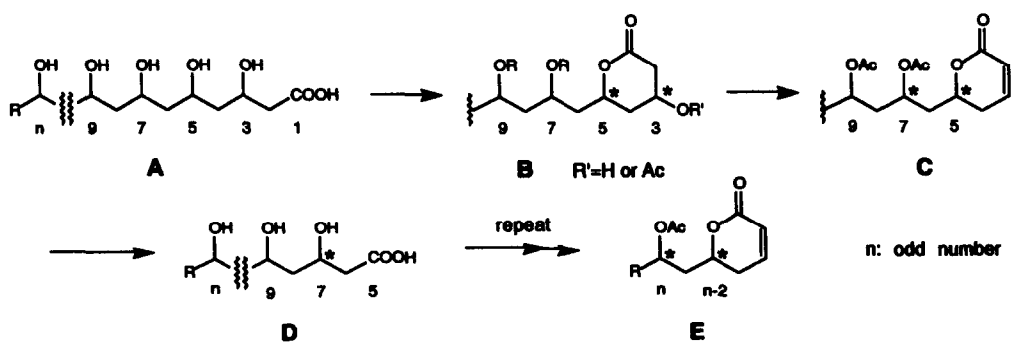
Abstract: A general and efficient strategy for determining the relative and absolute configurations of 1,3-polyhydroxyl functions is described.

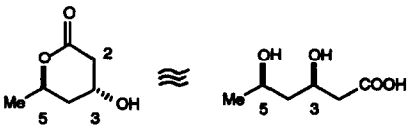
The polyene macrolide antibiotics have attracted much attention for their potent fungicidal properties and unique structure. A characteristic structural feature of these antibiotics is that they involve 1,3-polyol and all-trans-polyene moieties as exemplified by dermostatin A (**1**). Although a number of compounds is known to belong to this class of antibiotics, the complete stereostructure has not been elucidated yet except for a few cases.[1] We now report a general and efficient strategy for determining the relative and absolute configurations of polyhydroxyl functions in the extended 1,3-polyol chain.



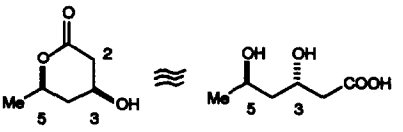
Dermostatin A (1)

1,3-Polyhydroxy carboxylic acid **A** is derivable from natural antibiotics through cleavage of the macro-ring using a suitable oxidative method and can be converted to lactone **B** and α,β-unsaturated lactone **C**, successively. Differentiation of 3,5-syn-**B** and its 3,5-anti-isomer can be achieved easily by analyzing the ^{1}H-NMR spectra since both chemical shifts and coupling constants of axial- and equatorial-like protons at the C-2





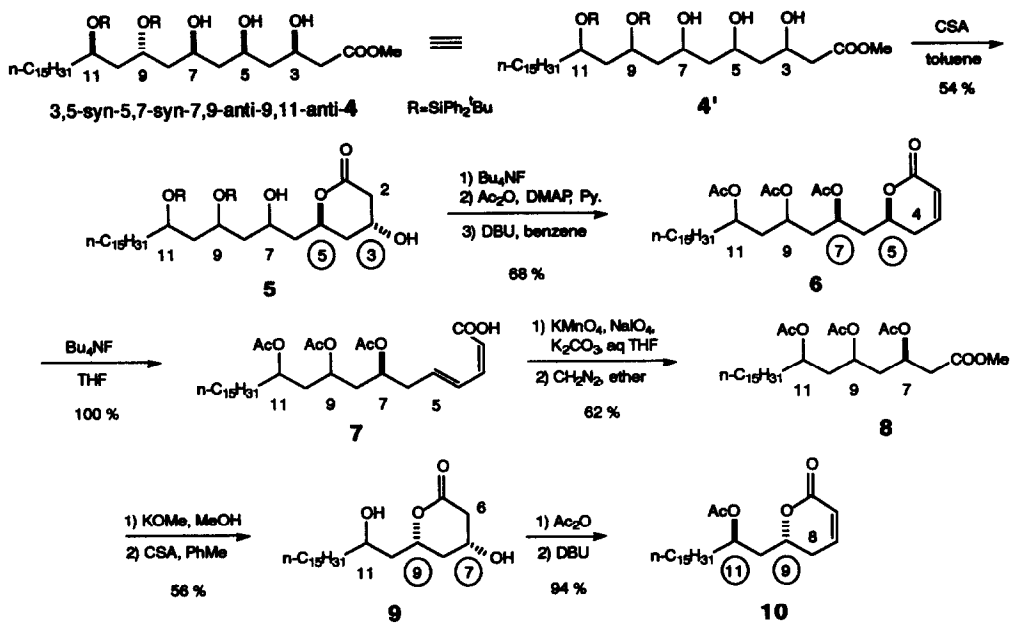
3,5-syn-**2**



3,5-anti-**3**

position of 3,5-syn-compound (cf. **2**) are different significantly from those of 3,5-anti-isomer (cf. **3**):[2,3] 3,5-syn-**2**,[4a] δ 2.62 (ddd, J=17.6, 3.7, 1.7 Hz; C_2-Heq), 2.73 (dd, J=17.6, 5.1 Hz; C_2-Hax), 3,5-anti-**3**,[4b] δ 2.46 (dd, J=17.1, 7.8 Hz; C_2-Hax), 2.90 (ddd, J=17.1, 5.9, 1.5 Hz; C_2-Heq). The relative configuration at C-5 and C-7 in lactone **C** can also be determined based on a structure-specific ^{1}H NMR splitting pattern[5] recently reported by us; in 5,7-syn-isomer **C**, signals of C-4 protons appear separately at δ 2.29 ~ 2.33 and δ 2.45 ~ 2.53, while in 5,7-anti-**C**, the corresponding signals appear overlapped at ca. δ 2.35. Thus, it is possible to determine the relative configurations at three chiral centers (C-3, C-5, and C-7) in **A** by simple operations. Conversion of lactone **C** leads to carboxylic acid **D** having the same β-hydroxy acid structure as **A** and thus the same sequence of reactions (**A** → **B** → **C**) is reiterative eventually determining the relative configurations of all of the remaining hydroxyl groups. The absolute stereostructure of 1,3-polyol **A** can also be determined from the $[\alpha]_D$ or CD value of α,β-unsaturated lactone **C** or **E**.

The generality of the present strategy was firmly confirmed using a stereochemically well-defined compound synthesized by the authenticated method.[6] Racemic 3,5-syn-5,7-syn-7,9-anti-9,11-anti-pentaol derivative **4**[7,8] was chosen as the starting material in order to demonstrate the effectiveness of the present methodology since **4** involves all possible combination of stereoisomers. The present work was undertaken supposing that the stereostructure of **4** was unknown (cf. **4'**). Treatment of the carboxylic acid **4'** with CSA in toluene gave lactone **5** in 54% yield along with the recovered **4'** (19%). The relative configuration at C-3 and C-5 was determined as syn, since signals of C-2 protons in **5** appeared at δ 2.60 (ddd, J=17.3, 3.9, 1.5 Hz) and 2.70 (dd, J=17.3, 5.1 Hz). Removal of the silyl group in **5** with n-Bu_4NF, acetylation with Ac_2O, and DBU treatment yielded α,β-unsaturated lactone **6** in 68% yield. Signals of C-4 protons in **6** appeared separately at δ 2.30 (dddd, J=18.3, 11.7, 2.4, 2.4 Hz) and 2.51 (dddd, J=18.3, 6.1, 3.9, 1.0 Hz), which suggested the 5,7-syn-configuration. The previously reported n-Bu_4NF-induced ring-opening of α,β-unsaturated δ-lactone[9] was effectively applied for the crucial conversion of **6** into ester **8**. Treatment of **6** with excess n-Bu_4NF in THF gave dienoic acid **7** quantitatively without causing hydrolysis of the acetoxyl groups.[10] Oxidation of **7** with $KMnO_4$-$NaIO_4$[11] followed by diazomethane treatment afforded methyl ester **8** in 62% yield. Then, the same reaction sequence mentioned above was repeated. The triacetoxy ester **8** was, after hydrolysis of the acetoxyl groups with KOMe in MeOH (70%), converted into lactone **9** in 80% yield. Acetylation of **9** and subsequent DBU treatment produced α,β-unsaturated lactone **10** in 94% yield. Signals of C-6 protons in **9** appeared at δ 2.48 (dd, J=17.1, 7.6 Hz) and 2.91 (ddd, J=17.1, 5.9, 1.2 Hz) and those of C-8 protons in **10**



appeared overlapped at δ 2.35, exhibiting the typical patterns for 7,9-anti- and 9,11-anti-configurations, respectively. Thus, the relative configuration of the racemic 3,5,7,9,11-pentaol derivative **4'** was determined as 3,5-syn-5,7-syn-7,9-anti-9,11-anti, which is consistent with the structure **4**. It should be emphasized that signals of protons used for determining the relative configuration of **4'** (methylene protons at C-2 in **5**, C-4 in **6**, C-6 in **9**, and C-8 in **10**) were clearly observed without overlapping with those of the other protons, which made the assignment of these signals unequivocal.

If the starting **4** is optically active, then the absolute stereostructure should in principle be determined by measuring $[\alpha]_D$ or CD of lactone **6** or **10**.[12]

The stereostructure of pentamycin, a polyenemacrolide antibiotic, has been determined recently based on the present strategy,[13] which will be reported in due course.

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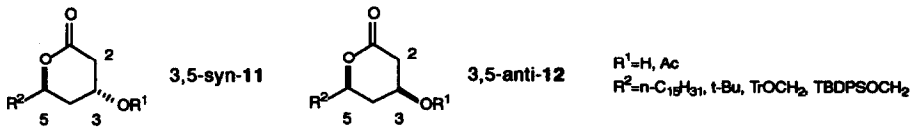
2. The same ^{1}H NMR patterns were observed in the related lactones (**11** and **12**) and their acetates of known stereostructure: e.g., 3,5-syn-**11** (R^1=Ac, R^2=n-$C_{15}H_{31}$): δ 2.71 (ddd, J=18.1, 3.7, 1.5 Hz), 2.79 (dd, J=18.1, 5.1 Hz), 3,5-anti-**12** (R^1=Ac, R^2=n-$C_{15}H_{31}$): δ 2.57 (dd, J=17.1, 6.6 Hz), 2.92 (ddd, J=17.1, 6.4, 1.0 Hz).



Configurations of C_5-R^2 and C_3-OH groups in the related δ-lactone moiety of compactin have proved to be equatorial and axial, respectively, by X-ray analysis.[14a] Its NMR data are compatible to those of lactones shown here.[14b]

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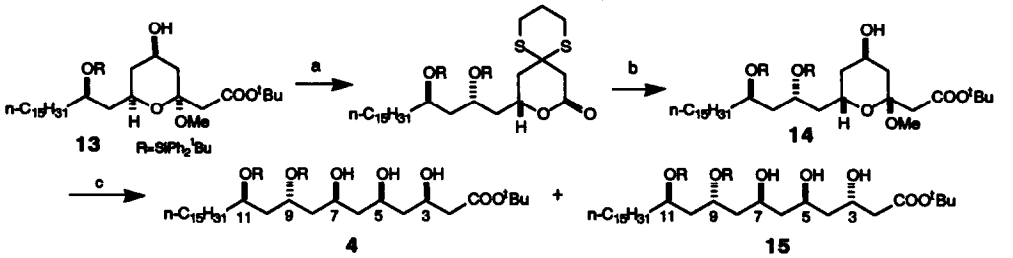
7. Only one enantiomer of the racemic **4** is shown.
8. The compound **4** was synthesized starting from **13**.[5] Cleavage of the acetal ring of **14** followed by $NaBH_4$ reduction afforded a mixture of **4** and **15**. At this stage, the configurations at C-3 positions of two isomers can not be determined. The less polar ester producing δ-lactone having C_3-ax OH group ($W_{h/2}$=10 Hz; C_3-H) was assigned as **4**.



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10. Retaining of the acetoxyl function is helpful in isolating the ring-opened product **7** and subjecting it to further oxidative cleavage.
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12. When **10** exhibits the positive sign of $[\alpha]_D$[15] and/or positive Cotton effect in CD,[16] the absolute configuration at C-9 should be R. Thus, the absolute configurations at all chiral centers in **4** can be shown as 3R, 5R, 7R, 9S, and 11R.
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