Chiral synthetic block based on (*R*)-pantolactone

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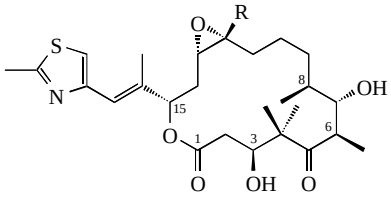
The synthesis of (*R*)-(+)-2,2-dimethyl-4-(1,1-dimethyl-2-oxo-1-butyl)-1,3-dioxolane from (*R*)-pantolactone has been developed.

Among antineoplastic agents, 16-membered epothilones (A, B, C, D…)[1,2] and their analogues are of particular interest as potential drug candidates.[3,4] Synthetic approaches to epothilones and structure–activity relationships were considered in detail in the reviews.[5–8]



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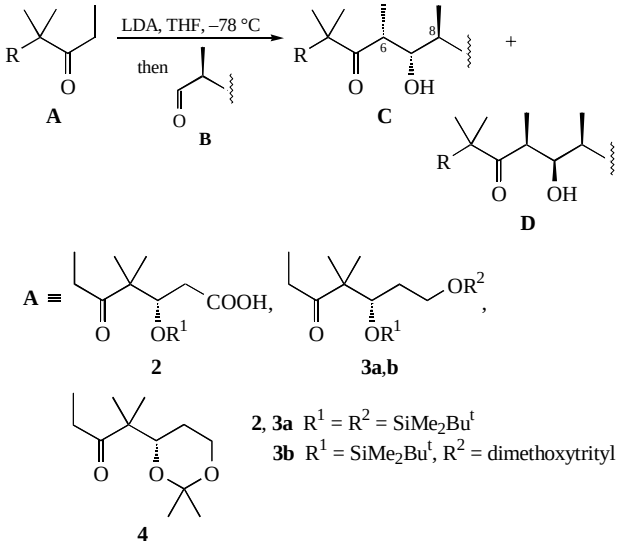
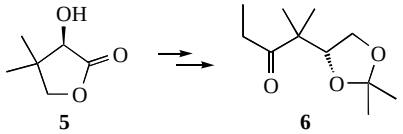
Epothilone A, R = H
Epothilone B, R = Me

In the synthesis of epothilones, the construction of a C^1–C^9 polypropionate moiety saturated with chiral centres, in particular, its C^6–C^8 fragment, seems the most difficult problem. Usually, this problem is solved using the aldol condensation of the enolates of appropriately functionalised ketones **A** with aldehydes **B** to obtain the correct (*syn*,*anti*)-stereochemistry of the C^6–C^8 fragment of blocks **C**. The use of dienolates of keto acid **2**,[9] its derivatives[10,11] and **3a**[12] as compounds **A** is accompanied by the formation of considerable amounts (from 3:1 to 1:1) of undesirable *syn*,*syn*-diastereomer **D** (Scheme 1), although it provides the rapid construction of the bottom hemisphere of epothilones. In contrast, blocks **C** can be prepared with high diastereoselectivity by the reaction of ketone enolates **3b**[13] and **4**[14,15] with **B**. Note that approaches to epothilones with the participation of **2**–**4** lead to the key precursors of the strategies of C^1–C^{15} macrolactonization,[9] C^{12}–C^{13}-olefin metathesis *etc*.[5,6]

In this work, we propose the use of chiral *gem*-dimethyl-containing ketoacetonide **6** prepared from (*R*)-pantolactone **5**† (Scheme 2) for the induction of chirality in the C^6–C^8 site of such structures **C** followed by the development of C^2–C^3-macrocyclisation[16] strategies.

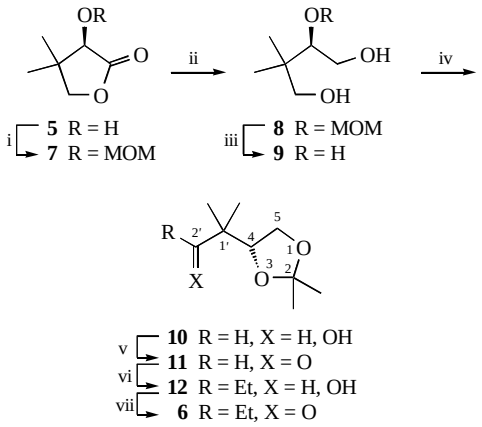


Scheme 1



Scheme 2

To prepare compound **6**, the MOM derivative of (*R*)-pantolactone **7** was converted into triol **9** by exhaustive reduction with $LiAlH_4$ through diol **8** and the methanolysis of the latter. Direct reduction of **7** to **9** with $LiAlH_4$ is experimentally difficult to perform and gives the triol[17] with impurities (according to the value of $[\alpha]_D^{20}$). Next, triol **9** was entered into the H^+-catalysed reaction with acetone; acetonide **10** was oxidised with Collins' reagent; aldehyde **11** was condensed with EtMgBr, and the resulting diastereomer mixture of alcohols **12** was treated with PDC to obtain target ketoacetonide **6** (Scheme 3).



Scheme 3 *Reagents and conditions*: i, 1.2 equiv. $ClCH_2OMe$, 1.2 equiv. $EtNPr^i_2$, CH_2Cl_2, 40 °C, 20 h, 96%; ii, 2.0 equiv. $LiAlH_4$, THF, 20 °C, 12 h, 88%; iii, MeOH, *p*-toluenesulfonic acid cat., 20 °C, 12 h, 98%; iv, Me_2CO, *p*-toluenesulfonic acid cat., 20 °C, 12 h, 91%; v, excess $CrO_3 \cdot 2Py$, CH_2Cl_2, 20 °C, 3 h, 60%; vi, 1.5 equiv. EtMgBr, THF, 0 °C, 1.5 h, 60%; vii, 1.5 equiv. pyridinium dichromate (PDC), CH_2Cl_2, 0 °C, 1.5 h, 51%.

† (*R*)-Pantolactone (Ufa) with *ee* ≥ 99% was used in this work. As found from the ^1H NMR spectra measured in the presence of (+)-Eu(hfc)$_3$, compound **6** exhibited *ee* 100%.

The NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 (^1H) and 75.47 MHz (^{13}C); TMS was used as an internal standard. Optical rotations were measured on a Perkin-Elmer M-141 polarimeter at 25 °C.

(4R)-(+)-2,2-Dimethyl-4-(1,1-dimethyl-2-oxobut-1-yl)-1,3-dioxolane **6**: colourless oil, $[\alpha]_D^{20}$ +8.0 (*c* 0.4, MeOH). ^1H NMR ($CDCl_3$) δ: 0.97 (t, 3H, Me, *J* 7.2 Hz), 1.07 and 1.14 (s, 6H, 1′-Me_2), 1.28 and 1.35 (s, 6H, 2-Me_2), 2.51 (q, 2H, 3′-CH_2, *J* 7.2 Hz), 3.61 and 3.98 (2dd, 2×1H, 5-CH_2, *J* 6.8 and 7.0 Hz), 4.23 (t, 1H, 4-CH, *J* 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 7.66 (Me), 19.91 and 20.44 (1′-Me_2), 24.59 and 26.03 (2-Me_2), 31.23 (3′-C), 49.43 (1′-C), 65.54 (5-C), 79.64 (4-C), 108.61 (2-C), 214.99 (2′-C). Found (%): C, 65.63; H, 10.00. Calc. for $C_{11}H_{20}O_3$ (%): C, 65.97; H, 10.07.

(2R)-(–)-3,3-Dimethylbutane-1,2,4-triol **9**: mp 55–57 °C (ethyl acetate). $[\alpha]_D^{20}$ –15.85 (*c* 0.1, MeOH). ^1H NMR ($CDCl_3$) δ: 0.87 (s, 3H, Me), 0.92 (s, 3H, Me), 3.40 (d, 1H, 4-CH_2, *J* 10.8 Hz), 3.46 (d, 1H, 4-CH_2, *J* 10.8 Hz), 3.57 (t, 1H, 2-CH, *J* 7.7 Hz), 3.61 (dd, 1H, 1-CH_2, *J* 16.1 and 7.7 Hz), 3.64 (dd, 1H, 1-CH_2, *J* 16.1 and 7.7 Hz). ^{13}C NMR [$(CD_3)_2CO$] δ: 19.47 and 21.06 (2-Me_2), 37.66 (3-C), 62.42 (1-C), 69.09 (4-C), 76.93 (2-C).

Building block **6** is attractive from several standpoints. First, its synthesis is simple, and it can be applied to prepare enantiomers **6** (both enantiomeric (*R*)- and (*S*)-pantolactones with *ee* 99% are commercially available). Second, stereo control in the transition state to **C** can be improved (the chelating properties of a 1,3-dioxolane ring in **6** are better than those of 1,3-dioxane in **4**). Third, building block **6** as a new strategical subunit opens up new opportunities in the design and synthesis of epothilones and analogues (the acetonide moiety of **C** can be readily transformed into an aldehyde unit, and C^2–C^3 macrocyclisation can be performed).

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