

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

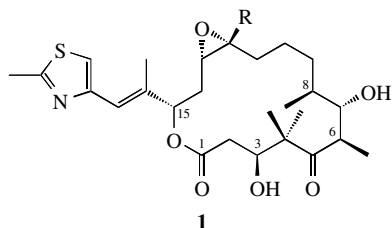
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The synthesis of (*R*)-(+)-2,2-dimethyl-4-(1,1-dimethyl-2-oxo-1-butyl)-1,3-dioxolane from (*R*)-pantolactone has been developed.

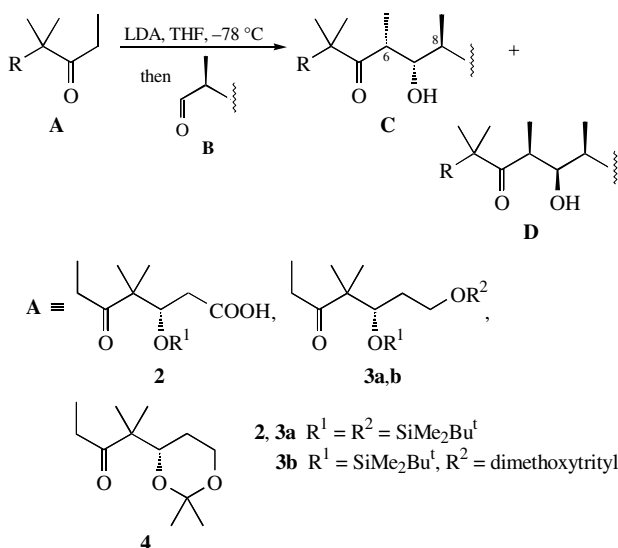
Among antineoplastic agents, 16-membered epothilones (A, B, C, D...) ^{1,2} and their analogues are of particular interest as potential drug candidates. ^{3,4} Synthetic approaches to epothilones and structure–activity relationships were considered in detail in the reviews. ^{5–8}



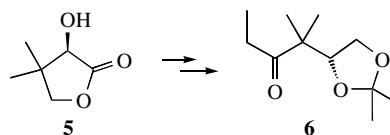
Epothilone A, R = H
Epothilone B, R = Me

In the synthesis of epothilones, the construction of a C¹–C⁹ polypropionate moiety saturated with chiral centres, in particular, its C⁶–C⁸ 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 C⁶–C⁸ 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 C¹–C¹⁵ macrolactonization, ⁹ C¹²–C¹³-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 C⁶–C⁸ site of such structures **C** followed by the development of C²–C³-macrocyclisation ¹⁶ strategies.

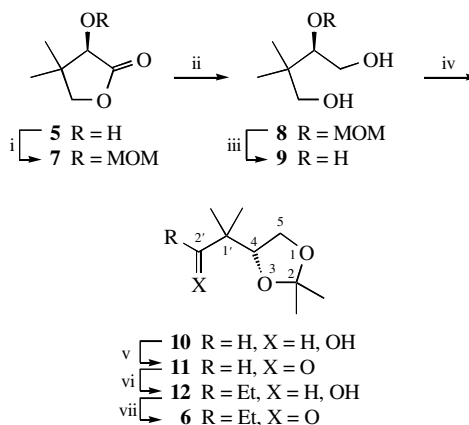


Scheme 1



Scheme 2

To prepare compound **6**, the MOM derivative of (*R*)-pantolactone **7** was converted into triol **9** by exhaustive reduction with LiAlH₄ through diol **8** and the methanolysis of the latter. Direct reduction of **7** to **9** with LiAlH₄ is experimentally difficult to perform and gives the triol ¹⁷ with impurities (according to the value of [α]_D²⁰). Next, triol **9** was entered into the H⁺-catalysed reaction with acetone; acetone **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. ClCH₂OMe, 1.2 equiv. EtNPr₃, CH₂Cl₂, 40 °C, 20 h, 96%; ii, 2.0 equiv. LiAlH₄, THF, 20 °C, 12 h, 88%; iii, MeOH, *p*-toluenesulfonic acid cat., 20 °C, 12 h, 98%; iv, Me₂CO, *p*-toluenesulfonic acid cat., 20 °C, 12 h, 91%; v, excess CrO₃·2Py, CH₂Cl₂, 20 °C, 3 h, 60%; vi, 1.5 equiv. EtMgBr, THF, 0 °C, 1.5 h, 60%; vii, 1.5 equiv. pyridinium dichromate (PDC), CH₂Cl₂, 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 (¹³C); TMS was used as an internal standard. Optical rotations were measured on a Perkin-Elmer M-141 polarimeter at 25 °C.

(4*R*)-(+)-2,2-Dimethyl-4-(1,1-dimethyl-2-oxobut-1-yl)-1,3-dioxolane **6**: colourless oil, [α]_D²⁰ +8.0 (*c* 0.4, MeOH). ¹H NMR (CDCl₃) δ: 0.97 (t, 3H, Me, *J* 7.2 Hz), 1.07 and 1.14 (s, 6H, 1'-Me₂), 1.28 and 1.35 (s, 6H, 2-Me₂), 2.51 (q, 2H, 3'-CH₂, *J* 7.2 Hz), 3.61 and 3.98 (2dd, 2×1H, 5-CH₂, *J* 6.8 and 7.0 Hz), 4.23 (t, 1H, 4-CH, *J* 6.8 Hz). ¹³C NMR (CDCl₃) δ: 7.66 (Me), 19.91 and 20.44 (1'-Me₂), 24.59 and 26.03 (2-Me₂), 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 C₁₁H₂₀O₃ (%): C, 65.97; H, 10.07.

(2*R*)-(-)-3,3-Dimethylbutane-1,2,4-triol **9**: mp 55–57 °C (ethyl acetate). [α]_D²⁰ –15.85 (*c* 0.1, MeOH). ¹H NMR (CDCl₃) δ: 0.87 (s, 3H, Me), 0.92 (s, 3H, Me), 3.40 (d, 1H, 4-CH₂, *J* 10.8 Hz), 3.46 (d, 1H, 4-CH₂, *J* 10.8 Hz), 3.57 (t, 1H, 2-CH, *J* 7.7 Hz), 3.61 (dd, 1H, 1-CH₂, *J* 16.1 and 7.7 Hz), 3.64 (dd, 1H, 1-CH₂, *J* 16.1 and 7.7 Hz). ¹³C NMR [(CD₃)₂CO] δ: 19.47 and 21.06 (2-Me₂), 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 C²–C³ macrocyclisation can be performed).

References

- 1 G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth and H. Reichenbach, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 156.
- 2 K. Gerth, N. Bedorf, G. Höfle, H. Irschik and H. Reichenbach, *J. Antibiotics*, 1996, **49**, 560.
- [doi:10.1002/anie.199900000](#) 3 P. W. Glunz, L. He, S. B. Horwitz, S. Chakravarty, I. Ojima, T.-C. Chou and S. J. Danishefsky, *Tetrahedron Lett.*, 1999, **40**, 6895.
- [doi:10.1002/anie.199900000](#) 4 T.-C. Chou, X.-G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. A. Savin, J. R. Bertinato and S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 15798.
- [doi:10.1002/anie.199900000](#) 5 K. C. Nicolaou, Y. He, F. Roschangar, P. N. King, D. Vourloumis and T. Li, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 84.
- [doi:10.1002/anie.199900000](#) 6 K. C. Nicolaou, A. Ritzen and K. Namoto, *Chem. Commun.*, 2001, **17**, 1523.
- 7 C. Wessjohann, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 715.
- [doi:10.1002/anie.199900000](#) 8 K.-H. Altmann, M. Wartmann and T. O'Reilly, *Biochim. Biophys. Acta*, 2000, **1470**, M79.
- [doi:10.1002/anie.199900000](#) 9 K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. Finlay and Z. Vang, *J. Am. Chem. Soc.*, 1997, **119**, 7974.
- [doi:10.1002/anie.199900000](#) 10 C. R. Harris, S. D. Kuduk, K. Savin, A. Balog and S. J. Danishefsky, *Tetrahedron Lett.*, 1999, **40**, 2263.
- [doi:10.1002/anie.199900000](#) 11 C. B. Lee, Z. Wu, X. Zhang, M. D. Chappell, S. J. Stachel, T.-C. Chou, Y. Guan and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 5249.
- 12 K. C. Nicolaou, F. Sarabia, M. Ray, V. Finlay, S. Ninkovic, P. N. King, D. Vourloumis and C. G. Nicolaou, *Chem. Eur. J.*, 1997, **3**, 1971.
- 13 D. Schinzer, A. Limberg and O. M. Böhm, *Chem. Eur. J.*, 1996, **2**, 1477.
- [doi:10.1002/anie.199900000](#) 14 R. E. Taylor, G. M. Galvin, K. A. Hilfiker and V. Chen, *J. Org. Chem.*, 1998, **25**, 9580.
- [doi:10.1002/anie.199900000](#) 15 K.-H. Altmann, G. Bold, G. Caravatti, A. Flörscheimer, V. Guagnano, and M. Wartmann, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2765.
- 16 D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *Angew. Chem.*, 1997, **109**, 775.
- [doi:10.1002/anie.199900000](#) 17 I. Shiina, J. Shibata, R. Ibuka, Y. Imai and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 113.

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