Pergamon

Tetrahedron Letters 41 (2000) 7697–7700

TETRAHEDRON LETTERS

Stereospecific synthesis of α,ω-*cis*- and α,ω-*trans*-disubstituted oxepanes

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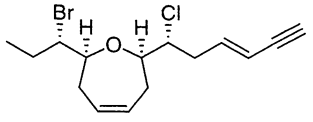
Received 13 July 2000; revised 3 August 2000; accepted 4 August 2000

Abstract

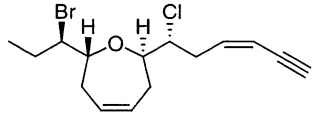
An efficient and versatile method for the stereospecific construction of α,ω-*cis*- and α,ω-*trans*-disubstituted oxepane skeletons is described. Cyclization of the hydroxy epoxides promoted by a $(Bu_3Sn)_2O$/$Zn(OTf)_2$ system proceeded via an S_N2 process and *exo* mode selectivity regardless of the configuration of the hydroxyl and the epoxy groups to provide the corresponding oxepanes in excellent yields. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: cyclization; epoxides; oxepanes; regioselection.

Oxepanes constitute a prominent structural feature of many natural products, represented by (+)-isolaurepinnacin (**1**)[1] and (+)-regioloxepane A (**2**) [2] (Fig. 1), isolated from the marine algae belonging to a variety of the *Laurencia* species. Much attention has been focused on efficient approaches toward this system.[3] In particular, the stereoselective introduction of alkyl substituents into the α- and ω-position of a cyclic ether possessing *cis*- or *trans*-orientation is an important synthetic goal. While some efficient methods toward stereoselective synthesis of α,ω-*cis*-oxepanes were developed,[4] few methods have been found for the α,ω-*trans*-oxepane system.[4f,m,5] We described an efficient protocol for the synthesis of oxepane via intramolecular opening of hydroxy epoxides promoted by a $(Bu_3Sn)_2O$/Lewis acid system in the proceeding article; this reaction proceeded via an S_N2 process and *exo* mode regardless of the geometry of



(+)-isolaurepinnacin (**1**)



(+)-rogioloxepane A (**2**)

Figure 1.

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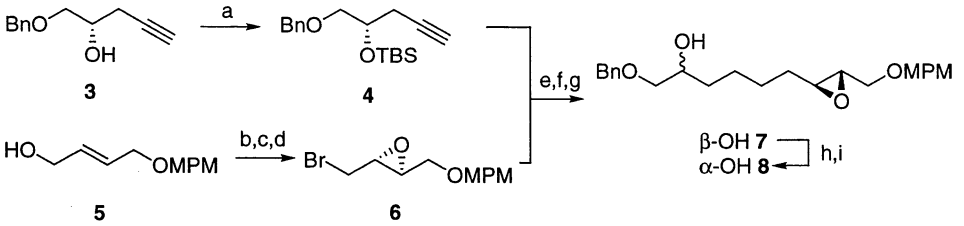
PII: S0040-4039(00)01344-7

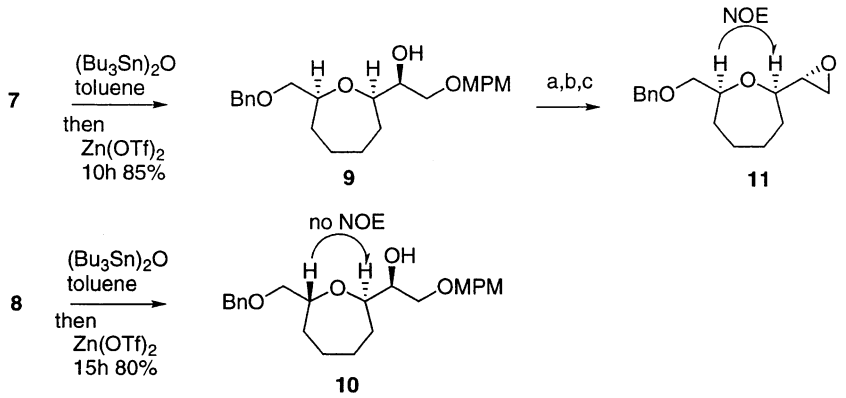
the epoxy group. We initiated the present work in an effort to explore the possibility of applying this methodology to the stereospecific construction of α,ω-*cis*- and α,ω-*trans*-oxepane skeletal systems.

The requisite key intermediate, hydroxy *trans*-epoxide **7** leading to α,ω-*cis*-oxepane, was prepared stereoselectively from the corresponding acetylene derivative **4**[6] and bromoepoxide **6**. The other intermediate **8** required for the preparation of the *trans*-analogue was obtained from the epoxy alcohol **7** via a Mitsunobu reaction[7] (Scheme 1).



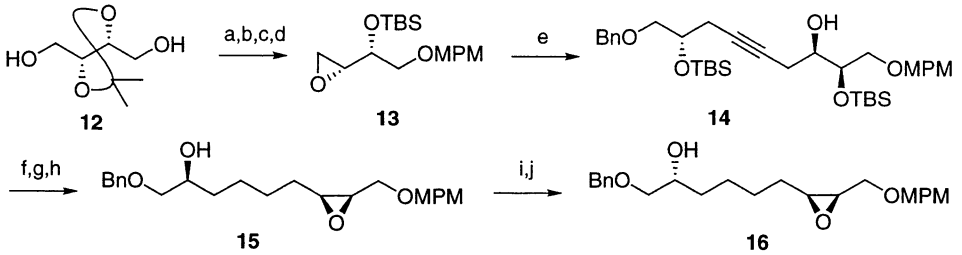
Scheme 1. *Reagents and conditions*: (a) TBSCl, NaH, THF, 100%; (b) TBHP, (+)-DET, $Ti(O^i\text{-}Pr)_4$, 4AMS, CH_2Cl_2, 93%, 89% ee; (c) TsCl, TEA, DMAP, CH_2Cl_2, 97%; (d) LiBr, DMF, 50°C, 94%; (e) *n*-BuLi, HMPA, THF, –30°C; (f) TBAF, THF, 52% (two steps); (g) H_2, Pd–C, AcOEt, 78%; (h) DEAD, PPh_3, $p\text{-}NO_2C_6H_4CO_2H$, THF, 98%; (i) K_2CO_3, MeOH, 96%

With the desired hydroxy *trans*-epoxides **7** and **8** in hand, we then proceeded with the stereospecific cyclization protocol. The tin ether prepared from **7** by reacting it with $(Bu_3Sn)_2O$ (0.6 equiv.) in refluxing toluene[8] was treated with $Zn(OTf)_2$ (0.4 equiv.) at 90°C. Under the conditions, the cyclization reaction proceeded smoothly to afford the corresponding α,ω-*cis*-oxepane **9** in 85% yield as the sole cyclic product. Similarly, the cyclization of the other isomer **8** proceeded with the same reactivity under the same reaction conditions to give the corresponding α,ω-*trans*-derivative **10** in 80% yield. The relative stereochemistry of the cyclized products **9** and **10** at the α,ω-positions with respect to each other was ascertained by NOE experiments. Further, the α,ω-*cis*-oxepane **9** was converted to its epoxide **11** to explore its NOE correlations in view of the overlapping of α-H and ω-H signals in the ^1H NMR spectrum (Scheme 2). It may be noted that the ready formation of terminal epoxide **11** from **9** confirms the earlier regioselective *exo* mode cyclization of **7** to the α,ω-*cis*-oxepane derivative **9**.

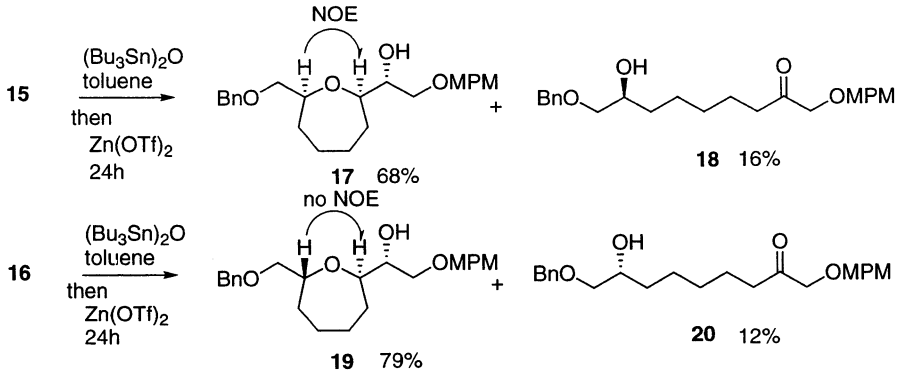


Scheme 2. *Reagents and conditions*: (a) MsCl, TEA, DMAP, CH_2Cl_2, 99%; (b) DDQ, CH_2Cl_2, H_2O; (c) K_2CO_3, MeOH, CH_2Cl_2, 85% (two steps)

Next, we turned our investigation to probe the reactivity of *cis*-epoxy substrates under the same reaction conditions. The desired cyclization precursors **15** and **16** were prepared by the protocol shown in Scheme 3. Epoxide **13** derived from 2,3-*O*-isoropylidene-D-threitol **12** was coupled with the acetylene derivative **4** by following the Yamaguchi method.[9] The resulting intermediate **14** was transformed to the hydroxy *cis*-epoxides **15** and **16** via standard procedures. Repeating the above-mentioned cyclization protocol on *cis*-epoxides **15** and **16** under identical reaction conditions provided, respectively, the corresponding α,ω-*cis*-oxepane **17** (68%) and its *trans*-isomer **19** (79%). It may also be noted that compared to the *trans*-epoxides **7** and **8**, there is a decrease in the reactivity of *cis*-epoxides **15** and **16**, and this property is reflected in the isolation of rearranged ketones **18** and **20** as minor products during the cyclization reaction (Scheme 4).



Scheme 3. *Reagents and conditions*: (a) MPMCl, NaH, DMF; (b) TsCl, TEA, DMAP, CH_2Cl_2, 72% (two steps); (c) Amberlyst 15, MeOH; (d) K_2CO_3, CH_2Cl_2, MeOH, 52% (two steps); (e) **4**, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, 60%; (f) H_2, Pd–C, AcOEt, 78%; (g) MsCl, TEA, DMAP, CH_2Cl_2; (h) TBAF, THF, 97% (two steps); (i) DEAD, PPh_3, *p*-$NO_2C_6H_4CO_2H$, THF, 95%; (j) K_2CO_3, MeOH, 95%



Scheme 4.

In conclusion, a highly efficient methodology for the stereospecific construction of α,ω-*cis*- and α,ω-*trans*-oxepanes, the fundamental structural unit of several important bioactive marine natural products, has been developed. Interestingly, the cyclization reaction proceeded via an S_N2 process and *exo* mode selectivity and independently of the hydroxyl and epoxide groups configuration in the substrate. Furthermore, the newly generated asymmetric centers are stereospecifically inducted in the product molecule. The oxepane derivatives **9**, **10**, **17** and **19**

inherited the requisite carbon skeleton and stereochemistry for its application to the synthesis of natural products (+)-isolaurepinnacin (**1**) and (+)-rogioloxepan A (**2**). Further efforts in this direction are in progress in our laboratory.

Acknowledgements

This work was financially supported in part by the Grant-in-Aid for Scientific Research on Priority Area No. 08245101 from the Ministry of Education, Science, Sports and Culture of the Japanese Government.

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