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Stereospecific rearrangement of α-hydroxyepoxide: efficient approach to the *trans*-bicyclo[9.3.0]tetradecane core en route to clavulactone

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Abstract—We document a synthetic route to *trans*-bicyclo[9.3.0]tetradecanes. The strategy is based on a quantitative and stereospecific Lewis acid mediated rearrangement of α-hydroxyepoxide to β-hydroxyketone, which paved the way for the synthesis of clavulactone and clavirolides.

Clavulactone and clavirolides A–F are novel tricyclic diterpenoids of the dolabellane family isolated from the Pacific soft coral *Clavularia viridis* collected off the Xisha Islands in the South China Sea[1] (Fig. 1).

Clavulactone and clavirolides A–F possess interesting and diverse biological activities,[1b] including cytotoxicity toward carcinoma cells, blockage of Ca^{2+} channels, negative inotropic activity as well as bradycardia effect. The unusual *trans*-bicyclo[9.3.0]tetradecane framework, biological significance, as well as the limited availability of these compounds have rendered them interesting targets to synthetic laboratories.[2] In a previous paper,[2e] we have reported an enantioselective approach to the bicyclo[9.3.0] tetradecenone framework of clavulactone, the most prominent member of this family. Herein, we disclose our further efforts toward the total synthesis of clavulactone.

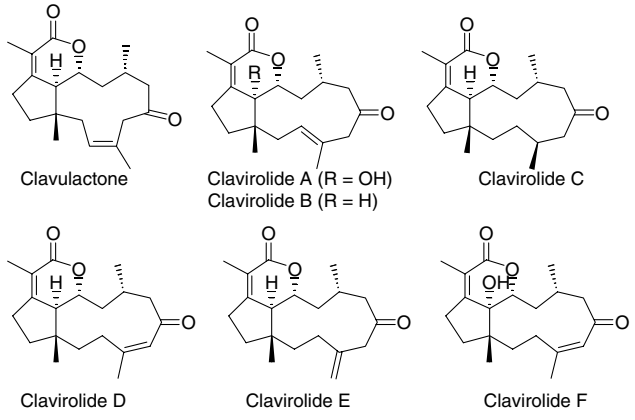

Figure 1. Clavulactone and clavirolides.

In view of the liability of the six-membered α,β-unsaturated lactone moiety, clavulactone **1** could be retrosynthetically reduced to the properly functionalized bicyclo[9.3.0] tetradecenone **3** through intermediate β-hydroxyketone **2**. Enone **3** could be prepared from the coupling/macro-cyclization sequence of allylic chloride **4** and protected cyanohydrin **5a**/**5b** (Scheme 1).

In our previous paper, we demonstrated the synthesis of bicyclo[9.3.0]tetradecenone **3** via ketone **8**.[2e] The segment coupling of cyanohydrin **5a** with allylic chloride **4** to ketone **8** was successful in terms of the conservation of the tethered (*Z*)-olefin in **8**; however, it fell short of efficiency due to the improper THP protection group. We report herein, an improved segment coupling of TBS protected cyanohydrin **5b** with **4** (Scheme 2). Aldehyde **6** was treated with TMSCN to give the TMS protected cyanohydrin followed by deprotection of TMS and THP to give diol **7**. Selective silylation of the primary hydroxyl group in **7** and protection of the secondary one with EVE afforded **5b**. Coupling between **4** (R = Bn) and **5b** was successfully realized in the

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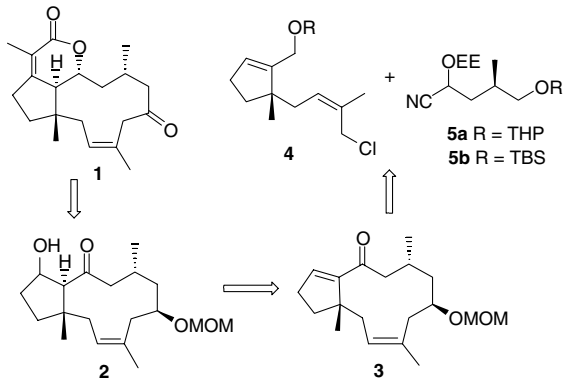
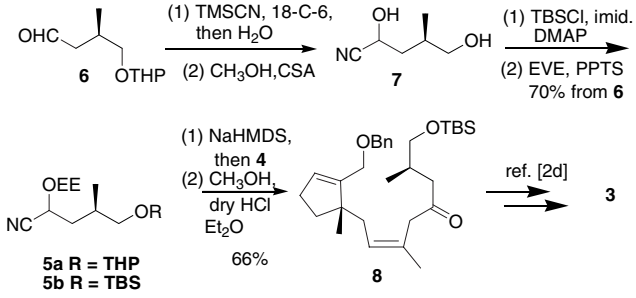


Scheme 1. Retrosynthetic analysis of clavulactone.



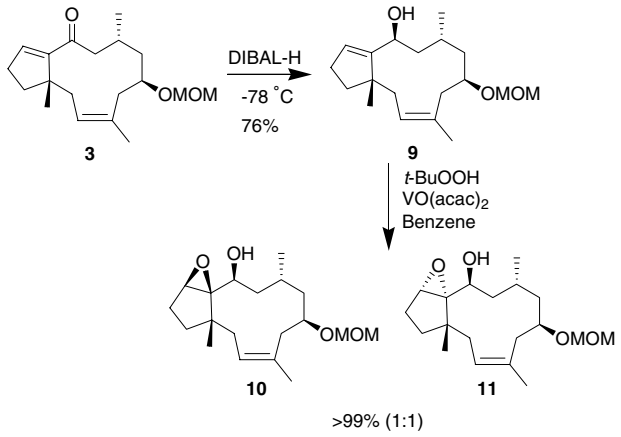
Scheme 2. Modified synthesis of ketone **8**.

presence of NaHMDS. Ketone **8** was obtained in 66% overall yield from **5b**, compared to 34% in the case of **5a**. Ketone **8** could be converted to **3** through a known pathway.[2e]

Enone **3** was subsequently reduced to allylic alcohol **9** with DIBAL-H in 76% yield. Although extensive 2D NMR studies including COSY, NOESY, DEPT, HMQC, and HMBC of **9** were performed, the configuration of the newly generated stereo center could not be determined at this time. Subsequent hydroxyl-directed epoxidation of **9** with *t*-BuOOH catalyzed by $VO(acac)_2$ delivered quantitatively two separable α-hydroxyepoxides, **10** and **11,** in an approximately 1:1 ratio. This negligible selectivity could be ascribed to the significant hindrance over the β-face of the double bond (Scheme 3).

Again the stereochemistry of the newly generated epoxide moiety of **10** and **11** could not be determined by 2D-NMR experiments. However, a significant NOE correlation was observed between hydrogens of the hydroxyl and the methyl group. Based on the data, we could assign the hydroxyl group in **10** and **11** as a β-OH, and so is the hydroxyl group in **9**. Selected NOE correlations were depicted in Figure 2.

It is known that α-hydroxyepoxides can rearrange in the presence of either Brönsted acids or Lewis acids to afford a variety of products, including triol via OH opening of the epoxide ring, β-hydroxyketone via hydrogen transfer, β-hydroxyketone via pinacol rearrangement, as well as products from extensive skeletal



Scheme 3. Synthesis of α-hydroxyepoxides **10** and **11**.

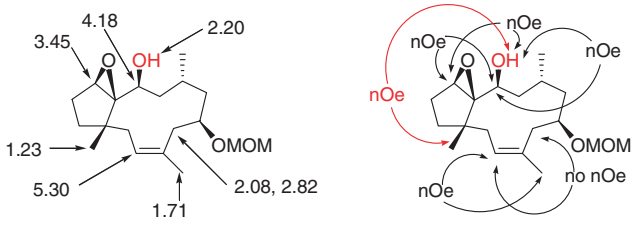
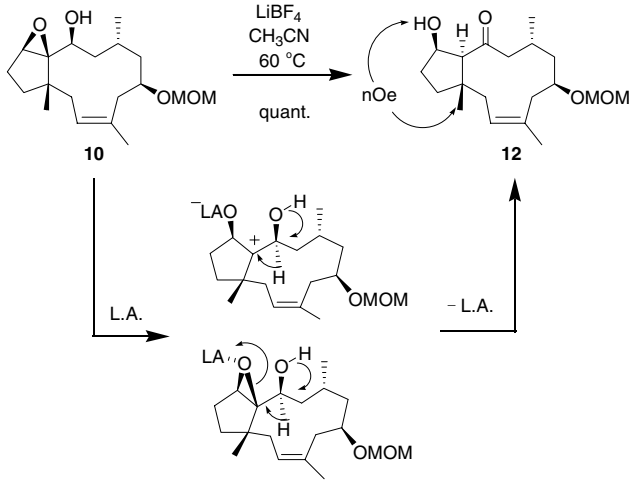
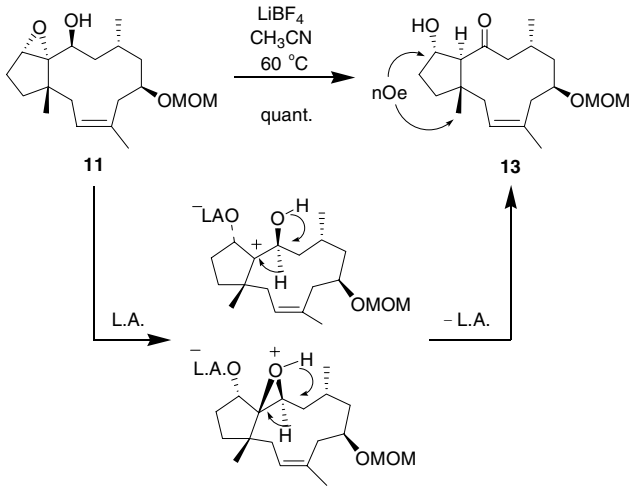


Figure 2. Selected NOE correlations of **10**.

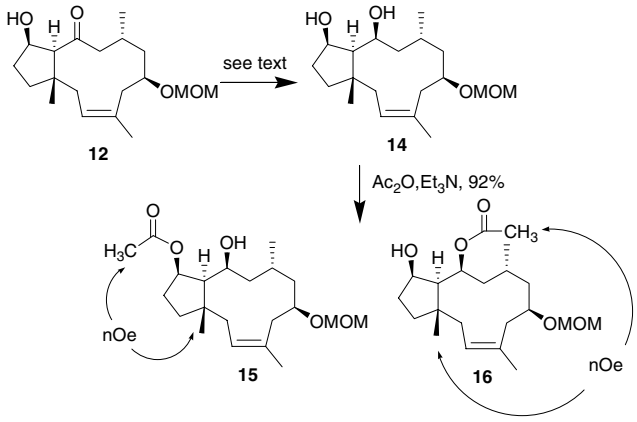
reformation, depending on the reaction conditions.[3] Considering the presence of MOM protection in our substrates **10** and **11**, application of Brönsted acids or strong Lewis acids as the catalysts for the rearrangement were precluded. A modest Lewis acid, $LiBF_4$, was attempted. When the mixture of **10** and catalytic amount of $LiBF_4$ in CH_3CN was maintained at 60 °C for 1 h, β-hydroxy ketone **12** was generated quantitatively and stereospecifically. No byproduct was detected. The stereochemistry of **12** was assigned by 2D NMR studies, and the result validated previous assignments for **10**. The transferring hydrogen opened the epoxide from the *anti*-face, which accounts for the stereochemistry of **12**. The rearrangement could be either stepwise or concerted (Scheme 4).



Scheme 4. Rearrangement of **10** and the possible mechanism.



Scheme 5. Rearrangement of **11** and the possible mechanism.



Scheme 6. Reduction of **12** and monoacetylation of **14**.

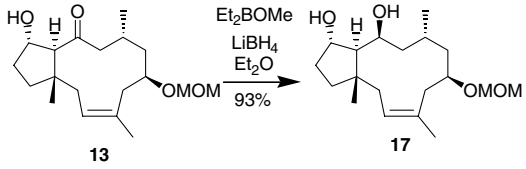
It is gratifying that such a transformation could recur in **11**, giving the desired β-hydroxyketone **13** quantitatively and stereospecifically. The stereochemistry of **13** was determined by 2D NMR studies, which confirmed the structure of **11**. The stereochemistry outcome indicated a possible process of *syn* opening of the epoxide; however, a more plausible mechanism for this rearrangement could be through a carbocation intermediate or a Payne intermediate,[3c] either of which would involve *anti* opening of the epoxide. Anyhow, the rearrangement should be stepwise (Scheme 5).

Hence, two β-hydroxyl ketones with the desired *trans*-bicyclo[9.3.0]tetradecane core were successfully prepared, which made it possible for further elaboration. The next task was to reduce the carbonyl group in **12** or **13** to the desired β-hydroxyl group on the macrocycle.

The outstanding reductive system developed by Evans et al., $(CH_3)_4NHB(OAc)_3/CH_3COOH/CH_3CN$, could convert β-hydroxyketones to 1,3-*anti*-diols with excellent diastereomeric selectivity.[4] When **12** was subject to the above system, however, 1,3-*syn*-diol **14** was obtained in 70% yield and no desired *anti*-diol product was detected. We also tried Tishchenko's conditions using *p*-nitrobenzaldehyde or acetaldehyde with catalytic SmI_2.[5] Substrate **12** was mostly recovered and no reaction occurred at all, probably due to the grave steric hindrance posed by the bicyclic ring system. Other attempts including systems $LiBH_4/LiBr/Et_2O$ and $LiBH_4/Et_2O$ were also dissatisfactory. The former system afforded **14** exclusively in 90% yield, while the latter provided a 2:1 diastereomeric mixture in 90% yield with **14** as the major product. The relative stereochemistry of diol **14** was determined via extensive 2D NMR studies of its monoacetyl derivatives **15** and **16** (Scheme 6).

Prasad and co-workers realized a highly 1,3-*syn* diastereoselective reduction of β-hydroxyketones by employing $Et_2BOMe/NaBH_4/CH_3OH/THF$ as the reductive reagents.[6] When **13** was treated with the above reagents, we obtained a 4:1 mixture in 93% overall yield. Utilization of $Et_2BOMe/LiBH_4/Et_2O$ did not alter the component ratio of the product, but accelerated the reaction (Scheme 7). The major product, obtained as crystals by recrystallization of the mixture from dichloromethane, was determined as 1,3-*anti*-diol **17** by an X-ray diffraction study (Fig. 3). This stereochemistry outcome of the reduction could be ascribed to the steric hindrance over the β face of the carbonyl group. Based on the crystallographic result of **17**, we confirmed our previous assignment of the stereochemistry of the OMOM group on the macrocycle as β in configuration.

In summary, we have developed a novel and efficient approach for the construction of *trans*-bicyclo[9.3.0] tetradecane core structure. By extensive spectral data studies, we assigned the stereochemistry of all the rearrangement products, which paved the way for the total synthesis of clavulactone. The strategy applied herein



Scheme 7. Reduction of **13**.

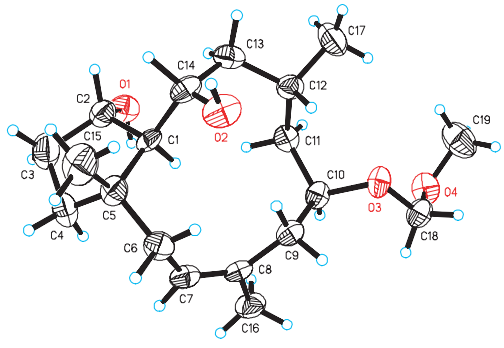


Figure 3. Molecular structure of compound **17** (Deposited Data—CCDC 287379).

could be readily adapted for the syntheses of clavirolides A–F. The focuses of future investigations will lie in the procurement of the precursors from **14** or **17**, and the ring closure of the six-membered α,β-unsaturated lactone. Studies are currently well underway in our laboratories.

Acknowledgements

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