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Model studies for the synthesis of clavulactone

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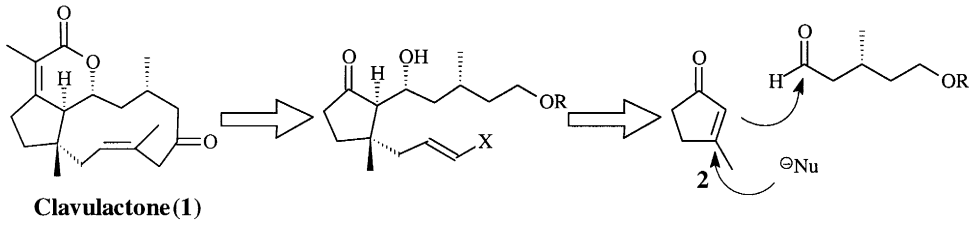
Abstract

A synthesis of the 5,6-bicyclic lactone core of clavulactone is described. The key step involves a tandem reaction of 3-methyl cyclopentenone with allyl *p*-tolyl sulfoxide and an aldehyde. The relative stereochemistry of the 5,6-bicyclic lactones **13a** and **13b** was confirmed by NMR studies.

Clavulactone **1**,[1a] isolated from *Clavularia viridis* collected from the Xisha Islands in the South China Sea, is one of the unique dolabellane diterpenes to be identified. Cytotoxicity assays showed that clavulactone was the most active on cultured Ehrlich ascites carcinoma (EAC) cells (ID_{50} 8 μg/ml).[1b] For these reasons clavulactone is an interesting target for total synthesis.

Our retrosynthetic analysis led to a trisubstituted cyclopentanone with a chiral quaternary carbon (Scheme 1). Obviously, for this segment one approach would be a three-component Michael-aldol strategy starting with 3-methyl cyclopentenone using an appropriate nucleophile. After considerable experimentation, the allylic *p*-tolyl sulfoxide developed by Hua[2] was chosen to introduce the quaternary carbon and to direct the subsequent aldol reaction. Herein we communicate our results.



Scheme 1.

The racemic sulfoxide **3** and valeraldehyde **4** were selected for model studies. The carbanion of **3** was produced by treatment with 1.05 equiv. LDA in THF at −78°C, then cyclopentenone **2** was added and the mixture was stirred for 30 min. Finally, the aldehyde **4** was added and the mixture was stirred for a further 10 min. After the usual work up, the main product was separated as a mixture of **5a**, **5b** and **6**. Compounds

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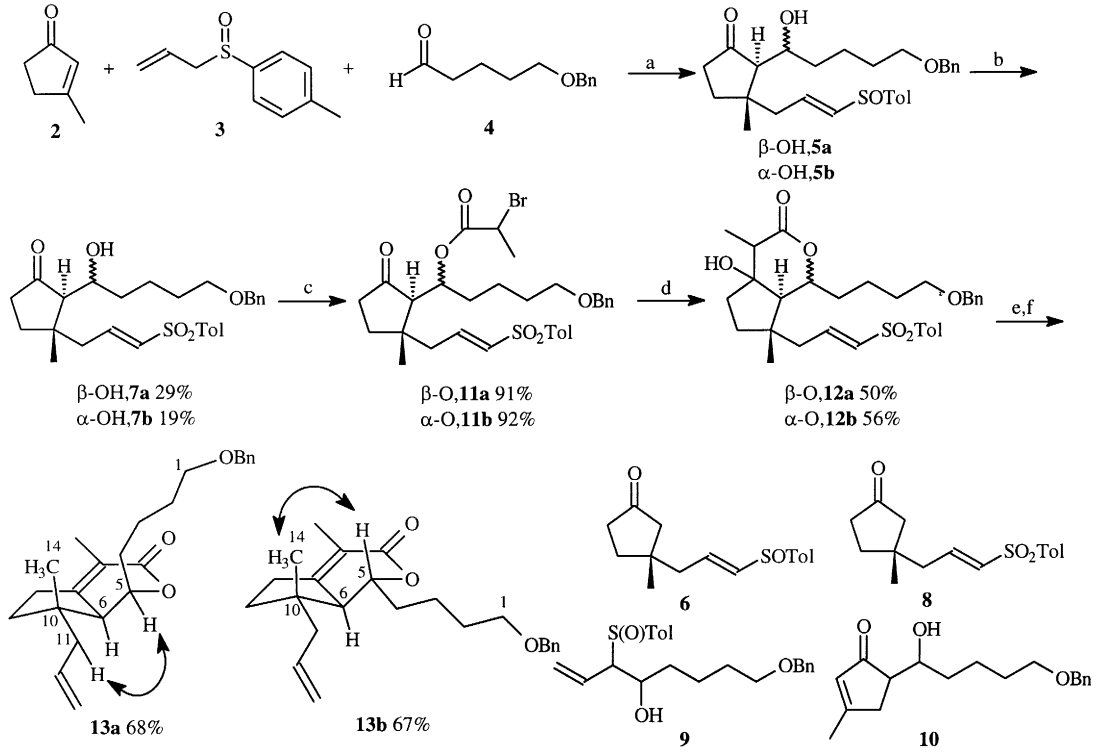
9 and **10** were also isolated in 10% yields. The formation of these products indicated that the Michael addition and aldol reaction were both reversible. It was found that prolonging the reaction led to more complicated results. After oxidation of the mixture of **5a**, **5b** and **6** with *m*-CPBA, the resultant sulfones **7a**, **7b** and **8** could be separated by chromatography in yields of 29%, 19% and 15%, respectively, in two steps.

With these products in hands, we diverted our attention to the determination of the relative configurations of the two β-hydroxycarbonyl compounds **7a** and **7b**. To resolve this question, we decided to construct the α,β-unsaturated lactone moiety which was required in the target molecule (Scheme 2). Bromopropionates **11** were prepared by acylation of **7a** or **7b** with α-bromopropionyl bromide in pyridine at 0°C in ca. 90% yields. Then, the intramolecular cyclization was carried out by diethylaluminum chloride/activated Zn[3] or samarium diiodide.[4] The results showed that SmI_2 was more preferable. Surprisingly, treatment of **11a** with SmI_2 gave only one isomer (**12a**), and **11b** led to a 2:1 isomeric mixture based on ^{1}H NMR analysis. These products were converted into **13a** and **13b**[6] via desulfonation and dehydration in 68% and 67% yields, respectively.



Scheme 2. Reagents and conditions: (a) LDA, THF, −78°C; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C; (c) 2-bromopropionyl bromide, pyridine, CH_2Cl_2, 0°C to rt; (d) SmI_2, THF, 0°C; (e) 6% Na (Hg), Na_2HPO_4, CH_3OH, 0°C; (f) methylsulfonyl chloride, DMAP, Et_3N, CH_2Cl_2, 0°C to rt

The NMR spectra of **13a** and **13b** were extensively examined. In the ^{1}H–^{1}H NOESY spectra of **13a** and **13b**, the observed intense correlation between H-11 (1.89 ppm) and H-5 (4.23 ppm) in **13a** suggested that H-5 and the allylic chain were *syn* to each other. On the other hand, in **13b**, the correlation between CH_3-10 (0.82 ppm) and H-5 (4.16 ppm) suggested that H-5 and 10-methyl group were *syn*. The above deduction was confirmed by ^{13}C spectra, the chemical shift of C-14 in **13a** (25.9 ppm) being at a lower field than that of C-14 in **13b** (19.6 ppm). Based on the δ effects of ^{13}C chemical shifts,[5] the $\Delta\delta$=+6.3

ppm value indicated that the methyl group and the upper chain in **13a** should be situated in a *syn*-diaxial orientation. The conformations of **13a** and **13b** are shown in Scheme 2.

In summary, the fully substituted bicyclic core of clavulactone was been elaborated via a Michael addition–aldol condensation sequence. Further study towards a total synthesis of clavulactone utilizing this strategy is now being conducted in our laboratory.

Acknowledgements

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2. Hua, D.-H.; Venkataraman, S.; Coulter, M.-J.; Sinai-Zingde, G. *J. Org. Chem*. **1987**, *52*, 719.
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6. Several compounds were characterized by spectroscopic methods. For example: **7a**: ^{1}H NMR: δ ($CDCl_3$): 7.76 (d, 2H, *J*=8.2 Hz); 7.33 (d, 2H, *J*=8.2 Hz); 7.32 (s, 5H); 7.01 (dt, 1H, *J*=14.9, 7.8 Hz); 6.38 (d, 1H, *J*=14.9 Hz); 4.49 (s, 2H); 3.80 (m, 1H); 3.49 (t, 2H, *J*=6.1 Hz); 2.68 (dd, 1H, *J*=14.0, 7.8 Hz); 2.50 (dd, 1H, *J*=14.0, 7.8 Hz); 2.43 (s, 3H); 2.23 (m, 2H); 2.00 (d, 1H, *J*=7.9 Hz); 1.9∼1.4 (m, 8H); 1.05 (s, 3H). MS (FAB): 507, 485, 377, 293, 154, 136. IR (film): 3522, 1732, 1454, 1316, 1285, 1144, 1087 cm^{-1}. Anal. calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49; found: C, 69.39; H, 7.76. **7b**: ^{1}H NMR: δ ($CDCl_3$): 7.76 (d, 2H, *J*=8.1 Hz); 7.34 (d, 2H, *J*=8.1 Hz); 7.32 (s, 5H); 6.96 (dt, 1H, *J*=14.9, 7.5 Hz); 6.36 (d, 1H, *J*=14.9 Hz); 4.48 (s, 2H); 3.69 (m, 1H); 3.46 (t, 2H, *J*=6.1 Hz); 2.45 (m, 1H); 2.44 (s, 3H); 2.28 (m, 3H); 1.93 (d, 1H, *J*=4.1 Hz); 1.8–1.2 (m, 8H); 1.01 (s, 3H). MS (EI): 467, 377, 375, 359, 293. IR (film): 3508, 1731, 1318, 1286, 1146, 1088 cm^{-1}. Anal. calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49; found (%): C, 69.14; H, 7.67. **13a**: ^{1}H NMR: δ ($CDCl_3$): 7.34 (m, 5H); 5.75 (m, 1H); 5.10 (m, 2H); 4.50 (s, 2H); 4.23 (m, 1H); 3.49 (t, 2H, *J*=5.7 Hz); 2.41 (m, 3H); 2.0–1.8 (m, 3H); 1.83 (s, 3H); 1.8–1.6 (m, 6H); 1.40 (dt, 1H, *J*=11.2, 10.8 Hz); 1.17 (s, 3H). ^{13}C NMR: δ ($CDCl_3$): 166.9, 162.1, 138.7, 133.9, 128.4, 127.8, 127.6, 120.0, 118.3, 79.4, 73.1, 70.4, 54.1, 44.5, 37.4, 36.2, 33.4, 29.7, 27.7, 25.9, 21.3, 12.9. MS (EI): 369, 368, 350, 327, 135, 91. IR (film): 2922, 2863, 1709, 1101 cm^{-1}. Anal. calcd for $C_{24}H_{32}O_3$: C, 78.23; H, 8.75; found: C, 78.39; H, 8.99. **13b**: ^{1}H NMR: δ ($CDCl_3$): 7.33 (m, 5H); 5.80 (m, 1H); 5.07 (m, 2H); 4.50 (s, 2H); 4.16 (m, 1H); 3.49 (t, 2H, *J*=5.0 Hz); 2.45 (m, 3H); 2.31 (dd, 1H, *J*=13.7, 7.5 Hz); 2.16 (dd, 1H, *J*=13.7, 7.2 Hz); 1.82 (s, 3H); 1.8–1.5 (m, 8H); 0.82 (s, 3H). ^{13}C NMR: δ ($CDCl_3$): 166.8, 162.0, 138.6, 134.2, 128.4, 127.7, 127.6, 120.0, 118.5, 80.2, 73.0, 70.3, 51.1, 45.7, 44.6, 37.2, 33.4, 29.6, 27.5, 21.4, 19.6, 12.9. MS (EI): 369, 368, 327, 309, 91. IR (film): 2955, 2864, 1711, 1101 cm^{-1}.