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The stereoselective total synthesis of (−)-cleistenolide

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ABSTRACT

The stereoselective total synthesis of (−)-cleistenolide is described employing the Barbier allylation, MacMillan α-hydroxylation, Stille–Gennari olefination, and $CeCl_3{\cdot}7H_2O$ mediated lactonization as key steps.

The *Cleistochlamys kirkii* oliver belongs to the family of an annonaceae species with its origins from Tanzania and Mozambique.[1] The extracts of which are used in traditional medicine as a remedy for the treatment of wound infections, rheumatism, and tuberculosis.[2] The annonaceous acetogenins are powerful phytochemicals that are found only in the plant family annonaceae and are known to exhibit a wide range of biological activities. They constitute one of the most rapidly growing classes of new natural products and offer exciting anthelminitic, antitumor, antimalarial, antimicrobial, antiprotozoal, and pesticidal activities. In 2007, Nkunya et al. have discovered two novel constituents, (−)-cleistenolide and cleistodienol from the annonaceae.[3]

The 5-hydroxy-α,β-unsaturated-δ-lactone structural motif is frequently found in many natural products, such as (−)-cleistenolide (**1**), (+)-goniotriol (**2**), (+)-crassalactone A (**3**), and (−)-altholactone (**4**) (Fig. 1). Due to their fascinating structural features and potential biological activity, the synthesis of these molecules has attracted many synthetic chemists. Consequently, there have been some reports on the total synthesis of 5-hydroxy-α,β-unsaturated-δ-lactone containing natural products.[4] However, only a few methods are reported for the total synthesis of the (−)-cleistenolide.[5]

As part of our interest on the total synthesis of biologically active molecules,[6] we herein report a novel strategy for the synthesis of (−)-cleistenolide (**1**) employing D-mannitol as a cost-effective and readily available precursor.

Our retro-synthetic analysis of (−)-cleistenolide (**1**) reveals that it could be synthesized by means of $CeCl_3{\cdot}7H_2O$ catalyzed lactonization of precursor **12**, which in turn could be prepared from compound **9** via the cis-olefination of the aldehyde. The intermediate **9** could be prepared from compound **5** through the Barbier allylation and MacMillan α-hydroxylation. The compound **5** could in turn be prepared from optically active D-mannitol using a known protocol (Scheme 1).

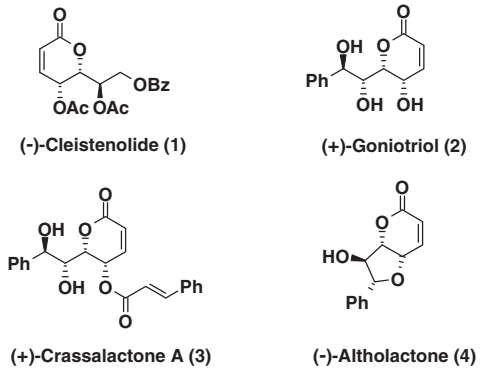

Figure 1. Examples of some 5-hydroxy-α,β-unsaturated-δ-lactone containing natural products.

Accordingly, the synthesis of target molecule (**1**) began from the commercially available D-mannitol. Initially, D-mannitol was converted into (*R*)-glyceraldehyde 1,2-acetonide **5** using a known protocol.[7] The zinc-mediated allylation of compound **5** in aqueous medium under Luche's[8] conditions gave the *anti*-homoallylic alcohol **6** in a highly diastereoselective manner (*syn*/*anti* = 5:95%). Protection of the resulting alcohol **6** with MOMCl in the presence of Hunig's base afforded MOM ether **7** in 92% yield. Dihydroxylation of compound **7** with OsO_4/NMO system followed by sodium periodate oxidation resulted in aldehyde **8**. Subsequent, α-amino-

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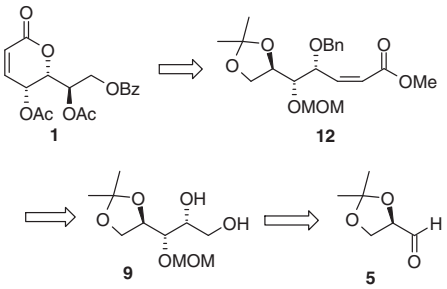
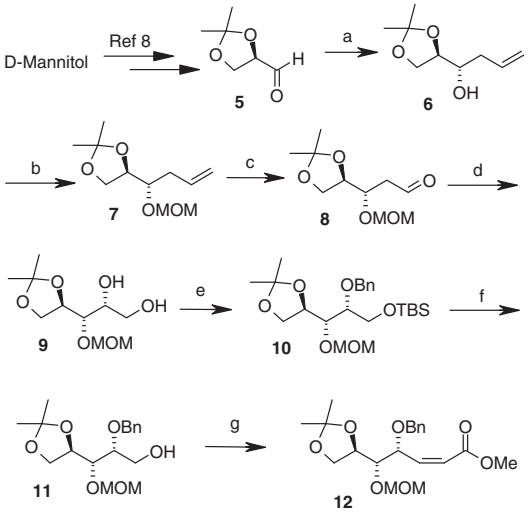


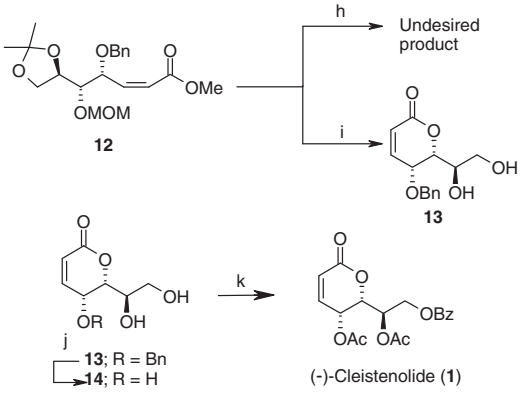
Scheme 1. Retrosynthetic analysis of (−)-cleistenolide (**1**).



Scheme 2. Reagents and conditions: (a) Zn, allyl bromide, THF, saturated solution of NH_4Cl (cat), 6 h, 90%; (b) DIPEA, MOMCl, DCM, 0 °C, 2 h, 92%; (c) (i) OsO_4 (0.5 mol %), NMO, acetone–H_2O, rt, 4 h; (ii) $NaIO_4$, rt, 2 h, 92%; (d) (i) D-proline, nitrosobenzene, DMSO; (ii) $NaBH_4$, MeOH, 0.5 h, 70% (over two steps); (e) (i) TBSCl, imidazole, DCM, 1 h, 91%; (ii) BnBr, NaH, TBAI, THF, 0 °C to rt, 2 h, 88%; (f) TBAF, THF, 0 °C to rt, 85%; (g) (i) IBX, DMSO/CH_2Cl_2, 90%, rt, 3 h; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, NaH, THF, 75%.

oxylation[9] of compound **8** with nitrosobenzene in the presence of D-proline at −10 °C, followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol. Treatment of aminooxy alcohol with 30 mol % $CuSO_4{\cdot}5H_2O$ afforded the chiral diol[10] **9** in 70% overall yield with 95% de. Monosilylation of diol **9** was achieved using TBSCl and imidazole. The resulting primary TBDMS ether was treated with benzyl bromide and NaH in THF, to furnish the benzyl ether **10**. Desilylation of compound **10** with TBAF resulted in the formation of primary alcohol **11** in 88% yield. Oxidation of **11** using IBX in DMSO/CH_2Cl_2 gave the aldehyde, which was subjected directly to a homologation under Still–Gennari conditions[11] to give (*Z*)-unsaturated ester, **12** in 75% yield with excellent stereoselectivity.

Interestingly, the deprotection of acetonide and MOM ether followed by lactonisation of **12** were achieved in one-pot using $CeCl_3{\cdot}7H_2O$ in CH_3CN at reflux conditions (Scheme 3).[12] On the other hand, treatment of **12** with *p*-TSA in methanol under acidic conditions gave the undesired product. Debenzylation of lactone **13** was achieved by $TiCl_4$ in dichloromethane at 0 °C to give the triol **14**. Finally, benzoyl protection of primary alcohol **14** followed by the acetylation of secondary alcohols gave the target molecule (−)-cleistenolide (**1**, Scheme 2). The spectroscopic and physical data (^1H and ^{13}C NMR, IR, $[\alpha]_D^{25}$) of compound (**1**) were identical in all respects to the data reported in the literature.[5,13]



Scheme 3. Reagents and conditions: (h) *p*-TSA, MeOH; (i) $CeCl_3{\cdot}7H_2O$, CH_3CN, reflux, 12 h, 65%; (j) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 30 min, 75%; (k) (i) BzCl, Et_3N, DMAP, 4 h, 92%; (ii) Ac_2O, Et_3N, DMAP, 24 h, 88%.

In summary, we have developed an efficient synthetic route for the stereoselective total synthesis of the (−)-cleistenolide starting from readily available D-mannitol. The synthetic strategy involves a tandem zinc-mediated allylation, MacMillan α-hydroxylation, Still–Gennari cis-olefination, and $CeCl_3{\cdot}7H_2O$ mediated lactonisation as key steps which allow the preparation of target molecule in an efficient way.

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13. Spectral data for compound **9**: colorless liquid, $[\alpha]_D^{25}$ +10.4 (*c* 0.25, $CHCl_3$): IR (neat): ν_{max} 3393, 2926, 2855, 1457, 1377, 1325, 1257, 1154, 1033, 846, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71 (q, *J* = 6.7 Hz, 2H), 4.20 (q, *J* = 6.0 Hz, 1H), 4.03–4.14 (m, 2H), 3.86–3.92 (m, 1H), 3.68–3.76 (m, 2H), 3.61–3.67 (m, 1H), 3.41 (s, 3H), 2.0 (s, 1H), 2.03 (s, 1H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.5, 98.3, 76.2, 67.2, 62.5, 55.3, 43.6, 42.7, 31.0. ESI-MS: *m*/*z*: 259 $(M+Na)^+$; HRMS calcd for $C_{10}H_{20}O_6Na$: 259.1157; found: 259.1151. Compound **13**: white semi-solid, $[\alpha]_D^{25}$ −84.8 (*c* 0.25, $CHCl_3$); IR (neat): ν_{max} 3424, 2926, 1723, 1585, 1402, 1341, 1261, 1092, 799, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.40 (m, 5H), 6.93–6.99 (m, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 4.68 (q, *J* = 10.9 Hz, 2H), 4.34–4.41 (m, 1H), 4.22–4.38 (m, 1H), 4.16–4.21 (m, 1H), 3.86–3.97 (m, 1H), 3.66–3.80 (m, 1H), 2.66–2.72 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 142.9, 128.6, 128.3, 127.9, 127.7, 124.0, 78.6, 71.8, 68.7, 65.4, 62.6. ESI-MS: m/z: 265 $(M+H)^+$; HRMS calcd for $C_{14}H_{17}O_5$: 265.1075; found: 265.1088. Compound **1**: colorless solid, mp 131–134 °C; $[\alpha]_D^{25}$ −152.3 (c 0.5,$CHCl_3$); IR (neat): ν_{max} 2965, 1728, 1454, 1369, 1260, 1215, 1125, 1086, 779, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 6.98 (dd, J = 9.5, 6.0 Hz, 1H), 6.30 (d, J = 9.7 Hz, 1H), 5.51 (ddd, J = 9.5, 4.2, 2.4 Hz, 1H), 5.40 (dd, J = 6.0, 2.6 Hz, 1H), 4.93 (dd, J = 12.5, 2.4 Hz, 1H), 4.80 (dd, J = 9.5, 2.6 Hz, 1H), 4.52 (dd, J = 12.5, 4.4 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.5, 165.8, 161.0, 139.8, 133.2, 129.7, 129.6, 128.4, 125.3, 75.6, 67.7, 62.1, 59.7, 20.6, 20.5; ESI-MS: m/z: 363 $(M+H)^+$. HRMS calcd for $C_{18}H_{19}O_8$: 363.1080; found: 363.1087.