Stereocontrolled synthesis of natural (−)-$\Delta^{9(12)}$-capnellene from a (−)-oxodicyclopentadiene

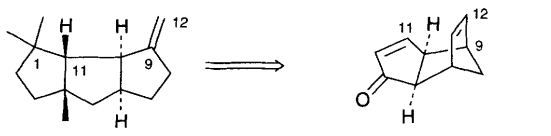
Keigo Tanaka and Kunio Ogasawara*†

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

(−)-$\Delta^{9(12)}$-Capnellene, a linear triquinane sesquiterpene isolated from the soft coral *Capnella imbricata*, has been synthesized stereoselectively in the natural enantiomeric form from an (−)-oxodicyclopentadiene.

Enantiocontrolled construction of (−)-$\Delta^{9(12)}$-capnellene[1] **1**, a linear triquinane sesquiterpene isolated from the soft coral *Capnella imbricata*, has not been disclosed to date although the asymmetric synthesis[2] of the unnatural (+)-enantiomer of **1** and two chiral approaches[3,4] to the key intermediate **9** of the racemic synthesis[5] have been reported.[6]‡ In this communication, we report the first stereocontrolled synthesis of natural (−)-$\Delta^{9(12)}$-capnellene **1** starting from (−)-oxodicyclopentadiene[7] **2** whose efficient preparation we have recently described.[8] The basis of the present synthesis is the structure and high functionality of the starting material, which led to the stereoselective construction of the requisite stereogenic centres on the triquinane framework without difficulty (Scheme 1).

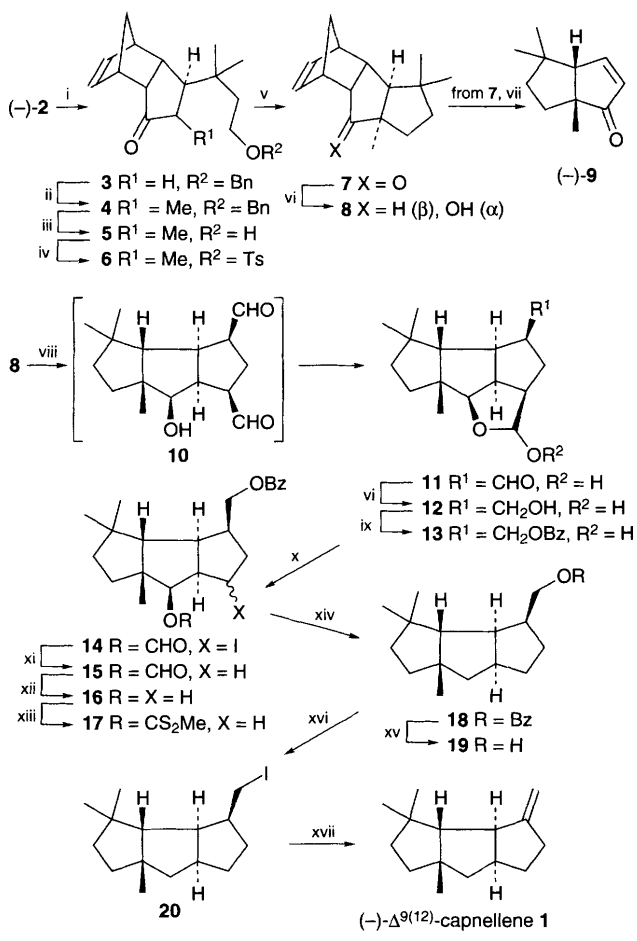
The synthesis began with stereoselective 1,4-addition of a tertiary Grignard reagent to the (−)-oxodicyclopentadiene **2** (>99% ee) to construct the C1–C11 bond of the target molecule **1**. The reaction proceeded stereoselectively from the convex face as expected. However, more than ten equivalents of 4-benzyloxy-2-chloro-2-methylbutane were needed to form enough Grignard reagent[4] to generate the 1,4-adduct **3** in a moderate yield. We overcame this difficulty by treating **2** directly with 1.5 equiv. of 4-benzyloxy-2-chloro-2-methylbutane and 3.0 equiv. of magnesium in refluxing diethyl ether in the presence of copper(I) bromide–dimethyl sulfide complex (0.05 equiv.) and 1,2-dibromoethane (0.2 equiv.) to give the adduct§ **3**, $[\alpha]_D^{26}$ −64.8 (*c* 1.1, $CHCl_3$), in 85% yield as a single isomer. Monomethylation of **3** was accomplished without formation of polyalkylated products by treatment with two equiv. of iodomethane in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) containing 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU, 3.0 equiv.) to give regioselectively the monomethyl ketone **4** (60%) as a mixture of epimers with recovery of 31% of the starting material **3**. Debenzylation of **4** followed by tosylation of the resulting alcohol **5** gave the tosylate **6** which was exposed to potassium *tert*-butoxide in THF to afford the tetracyclic ketone **7**, $[\alpha]_D^{29}$ −221 (*c* 1.0, $CHCl_3$), in 76% overall yield as a single isomer. To confirm its structure, **7** was heated in diphenyl ether (*ca.* 260 °C) for 30 min to effect a retro-Diels–Alder reaction to give the known bicyclic enone **9** (83%), $[\alpha]_D^{26}$ −179 (*c* 0.9, hexane) {lit., $[\alpha]_D^{25}$ −191 (*c* 0.57, hexane),[3] $[\alpha]_D^{20}$ −167.6 (*c* 0.95, hexane)},[4] with >99% ee,¶ whose racemate[5] has been transformed into racemic $\Delta^{9(12)}$-capnellene **1**.



(−)-$\Delta^{9(12)}$-capnellene **1** (−)-oxodicyclopentadiene (−)-**2**

Scheme 1

In order to establish the route to (−)-$\Delta^{9(12)}$-capnellene **1**, **7** was first reduced with diisobutylaluminum hydride (DIBAL) from the convex face. Although the reaction did not proceed in a completely stereoselective manner, the expected *endo*-alcohol **8** (92%), $[\alpha]_D^{29}$ +57.3 (*c* 0.8, $CHCl_3$), was obtained after separation of the minor *exo*-isomer (5%), $[\alpha]_D^{29}$ +58.7 (*c* 1.1, $CHCl_3$), by silica gel column chromatography. The double bond of **8** was then cleaved by sequential osmylation and periodate oxidation to generate the dialdehyde **10**, of which one formyl



Scheme 2 *Reagents and conditions*: i, $BnO(CH_2)_2C(Me)_2Cl$ (1.5 equiv.), Mg (3.0 equiv.), $CuBr{\cdot}SMe_2$ (cat.), Et_2O (85%); ii, LDA (2.0 equiv.), DMPU (3.0 equiv.), MeI (2.0 equiv.) (60%; 86% based on consumed **3**); iii, BBr_3, CH_2Cl_2; iv, *p*-TsCl, pyridine; v, Bu^tOK, THF, −78 °C (76% from **4**); vi, DIBAL, toluene, −78 °C (92%); vii, diphenyl ether, reflux (83%); viii, OsO_4 (cat.), NMO, pyridine, aq. THF, then $NaIO_4$ (91%); ix, PhCOCl, Et_3N, CH_2Cl_2 (97%); x, $PhI(OAc)_2$, I_2, *hv*, benzene, 20 °C (83%); xi, Bu_3SnH, 2,2′-azoisobutyronitrile (AIBN) (cat.), toluene, reflux (87%); xii, K_2CO_3, MeOH (99%); xiii, NaH, CS_2, THF, reflux, then MeI (96%); xiv, Bu_3SnH, AIBN (cat.), toluene, reflux (51% and 26% of **16**); xv, $LiOH{\cdot}H_2O$, MeOH–THF (95%); xvi, I_2, PPh_3, imidazole, MeCN–THF, reflux; xvii, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene, reflux (75% from **19**)

group formed spontaneously a cyclic hemiacetal to give the tetracyclic monoaldehyde **11** (91%), mp 95.5–97.0 °C. Having discriminated between the two formyl groups, we reduced the one remaining with DIBAL at −78 °C to give the primary alcohol **12** (81%), mp 154.5–156.5 °C, without affecting the hemiacetal. After benzoylation of **12**, the resulting benzoate **13** was subjected to photolysis[9] in the presence of iodosobenzene diacetate and iodine to afford the iodo formate **14** (83%) by oxidative cleavage of the remaining, masked, formyl group.

Having constructed the requisite carbon framework, we next removed extra functionalities from the tricyclic product **14** to yield the natural product. Thus, on sequential radical-initiated dehalogenation[10] and selective deformylation, **14** afforded the single hydroxybenzoate **16** (86%), $[\alpha]_D^{29}$ −36.9 (*c* 0.6, $CHCl_3$) *via* the diester intermediate **15**, $[\alpha]_D^{29}$ −53.6 (*c* 0.8, $CHCl_3$). Again employing a radical-initiated reaction,[11] the secondary hydroxy group of **16** was removed after transformation to the xanthate **17**, $[\alpha]_D^{27}$ −54.0 (*c* 1.3, $CHCl_3$), to give the benzoate **18**, $[\alpha]_D^{29}$ −13.0 (*c* 0.4, $CHCl_3$), in 49% overall yield from **16**, accompanied by 26% of the secondary alcohol **16**, which was recycled.

Transformation of **18** to the target molecule **1** was carried out in a straightforward manner in 71% overall yield in three steps. Thus, **18** was first debenzoylated to the primary alcohol **19**, mp 49.5–50.5 °C, $[\alpha]_D^{29}$ −1.4 (*c* 0.4, $CHCl_3$), which on sequential halogenation[12] and dehydrohalogenation yielded (−)-$\Delta^{9(12)}$-capnellene **1**, $[\alpha]_D^{29}$ −141.0 (*c* 0.1, $CHCl_3$) [lit., $[\alpha]_D^{20}$ −145 (*c* 0.4, $CHCl_3$) for the natural product;[1] $[\alpha]_D^{22}$ +149 (*c* 0.10, $CHCl_3$) for the unnatural enantiomer[2]] *via* the iodide **20**.

Footnotes

† E-mail c21799@cctu.cc.tohoku.ac.jp

‡ Asymmetric synthesis of (−)-**1** has been reported recently, see: T. Oshima, M. Sodeoka and M. Shibasaki, *116th Annual Meeting of the Pharmaceutical Society of Japan*, 1996, **2**, 90.

§ Satisfactory spectroscopic (IR, ^{1}H NMR, MS) and analytical (combustion and/or high resolution MS) data were obtained for all new isolable compounds.

¶ Optical purity was determined by HPLC using a chiral column (CHIRALCEL OD, eluted with Pr^iOH–hexane, 1 : 500).

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