

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

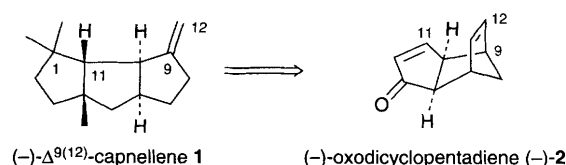
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(–)- $\Delta^{9(12)}$ -Capnellene, a linear triquinane sesquiterpene isolated from the soft coral *Capnella imbricata*, has been synthesized stereoselectively in the natural enantiomeric form from an (–)-oxodicyclopentadiene.

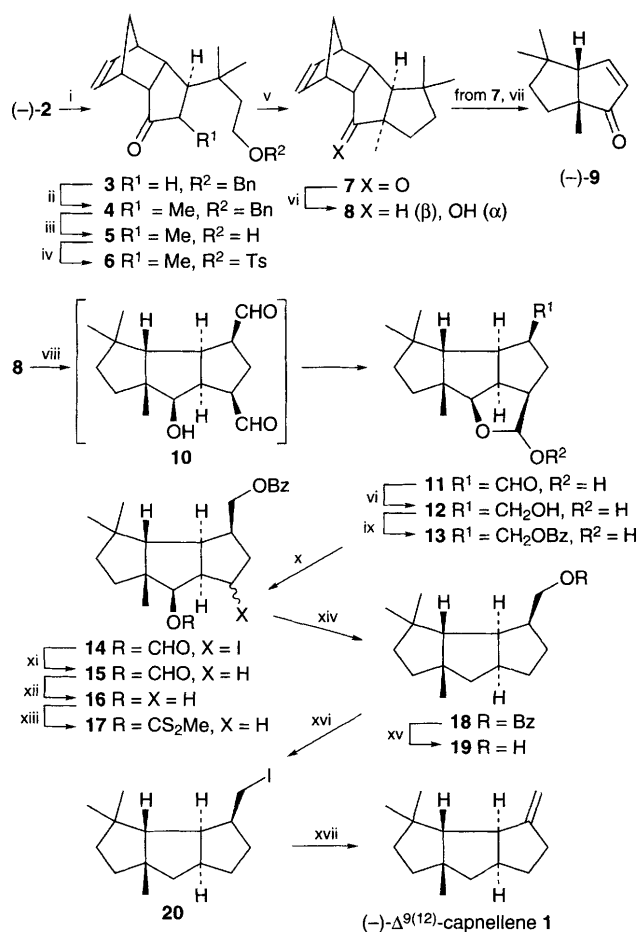
Enantiocontrolled construction of (–)- $\Delta^{9(12)}$ -capnellene¹ **1**, a linear triquinane sesquiterpene isolated from the soft coral *Capnella imbricata*, has not been disclosed to date although the asymmetric synthesis² of the unnatural (+)-enantiomer of **1** and two chiral approaches^{3,4} to the key intermediate **9** of the racemic synthesis⁵ have been reported.^{6‡} In this communication, we report the first stereocontrolled synthesis of natural (–)- $\Delta^{9(12)}$ -capnellene **1** starting from (–)-oxodicyclopentadiene⁷ **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 reagent⁴ 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, CHCl₃), 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*)-pyrimidinone (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, CHCl₃), 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 racemate⁵ has been transformed into racemic $\Delta^{9(12)}$ -capnellene **1**.



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, CHCl₃), was obtained after separation of the minor *exo*-isomer (5%), $[\alpha]_D^{29} +58.7$ (c 1.1, CHCl₃), 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(CH₂)₂C(Me)₂Cl (1.5 equiv.), Mg (3.0 equiv.), CuBr·SMe₂ (cat.), Et₂O (85%); ii, LDA (2.0 equiv.), DMPU (3.0 equiv.), MeI (2.0 equiv.) (60%; 86% based on consumed **3**); iii, BBr₃, CH₂Cl₂; 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, OsO₄ (cat.), NMO, pyridine, aq. THF, then NaIO₄ (91%); ix, PhCOCl, Et₃N, CH₂Cl₂ (97%); x, PhI(OAc)₂, I₂, hv, benzene, 20 °C (83%); xi, Bu₃SnH, 2,2'-azobisisobutyronitrile (AIBN) (cat.), toluene, reflux (87%); xii, K₂CO₃, MeOH (99%); xiii, NaH, CS₂, THF, reflux, then MeI (96%); xiv, Bu₃SnH, AIBN (cat.), toluene, reflux (51% and 26% of **16**); xv, LiOH·H₂O, MeOH–THF (95%); xvi, I₂, PPh₃, 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 benzylation of **12**, the resulting benzoate **13** was subjected to photolysis⁹ 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 dehalogenation¹⁰ and selective deformylation, **14** afforded the single hydroxybenzoate **16** (86%), $[\alpha]_{\text{D}}^{29} -36.9$ (c 0.6, CHCl₃) via the diester intermediate **15**, $[\alpha]_{\text{D}}^{29} -53.6$ (c 0.8, CHCl₃). Again employing a radical-initiated reaction,¹¹ the secondary hydroxy group of **16** was removed after transformation to the xanthate **17**, $[\alpha]_{\text{D}}^{27} -54.0$ (c 1.3, CHCl₃), to give the benzoate **18**, $[\alpha]_{\text{D}}^{29} -13.0$ (c 0.4, CHCl₃), 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, $[\alpha]_{\text{D}}^{29} -1.4$ (c 0.4, CHCl₃), which on sequential halogenation¹² and dehydrohalogenation yielded (–)- $\Delta^9(12)$ -capnellene **1**, $[\alpha]_{\text{D}}^{29} -141.0$ (c 0.1, CHCl₃) [lit., $[\alpha]_{\text{D}}^{20} -145$ (c 0.4, CHCl₃) for the natural product;¹ $[\alpha]_{\text{D}}^{22} +149$ (c 0.10, CHCl₃) for the unnatural enantiomer²] via the iodide **20**.

Footnotes

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‡ 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, ¹H 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 PrOH–hexane, 1:500).

References

- 1 E. Ayanoglu, T. Gebreyesus, C. M. Beechan, C. Djerassi and M. Kaisin, *Tetrahedron Lett.*, 1978, 1671.
- 2 A. I. Meyers and S. Bienz, *J. Org. Chem.*, 1990, **55**, 791.
- 3 H. R. Sonawane, B. S. Nanjundiah, V. G. Shah, D. G. Kulkarni and J. R. Ahuja, *Tetrahedron Lett.*, 1991, **32**, 1107; H. R. Sonawane, V. G. Naik, N. S. Bellur, V. G. Shah, P. C. Purohit, M. U. Kumar, D. G. Kulkarni and J. R. Ahuja, *Tetrahedron*, 1991, **47**, 8259.
- 4 M. Asaoka, K. Obuchi and H. Takei, *Tetrahedron*, 1994, **50**, 655.
- 5 E. Piers and V. Karunaratne, *Tetrahedron*, 1989, **45**, 1089.
- 6 Racemic syntheses of $\Delta^9(12)$ -capnellene, see: ref. 2; M. Ihara, T. Suzuki, M. Katogi, N. Taniguchi and K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, 1991, 644; *J. Chem. Soc., Perkin Trans. 1*, 1992, 865 and references cited therein.
- 7 A review on the natural product synthesis using a chiral oxodicyclopentadiene as chiral building block, see: K. Ogasawara, *J. Syn. Org. Chem. Jpn.*, 1996, **54**, 29.
- 8 Recent syntheses of chiral oxodicyclopentadiene; K. Tanaka and K. Ogasawara, *Synthesis*, 1995, 1237; T. Sugahara and K. Ogasawara, *Tetrahedron Lett.*, 1996, **37**, 205; T. Sugahara, Y. Kuroyanagi and K. Ogasawara, *Synthesis*, in the press.
- 9 R. Freire, J. J. Marrero, M. S. Rodriguez and E. Suarez, *Tetrahedron Lett.*, 1986, **27**, 383.
- 10 Cf. T. Imamoto, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 8, p. 793.
- 11 Cf. S. W. McCombie, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 8, p. 811.
- 12 P. G. Garegg and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, 1979, 978.

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