Asymmetric Heck Reaction: A Catalytic Asymmetric Synthesis of the Key Intermediate for $\Delta^{9(12)}$-Capnellene-3β,8β,10α-triol and $\Delta^{9(12)}$-Capnellene-3β,8β,10α,14-tetrol

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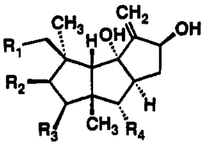
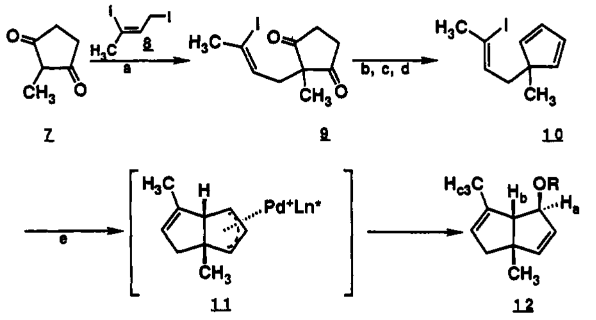
Summary: A catalytic asymmetric synthesis of the key intermediates **21** and **22** for the capnellenols has been achieved (80% ee) by an asymmetric Heck reaction followed by an anion capture process. Furthermore, an improved synthetic route to (±)-capnellenols has been also developed.

Capnellenols are sesquiterpene alcohols **1**–**6**, isolated from sun-dried colonies of the soft coral *Capnella imbricata*.[1] These substances appear to have protective roles against fish predation and invasion by microorganisms, larvae, and algae.[2] In 1986 we completed the first total syntheses of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**), (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**3**), (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol (**6**) using a Saegusa–Ito reaction as a key step, which required a stoichiometric amount of Pd(OAc)$_2$.[3] Herein we report a catalytic asymmetric synthesis of the key intermediates **21** and **22** for **3** and **6**, in which an asymmetric Heck reaction, followed by a regio- and stereocontrolled anion capture process, plays a key role to afford **21** and **22** in 80% ee.[4] This is the first example of an asymmetric Heck reaction followed by an anion capture process.[5]



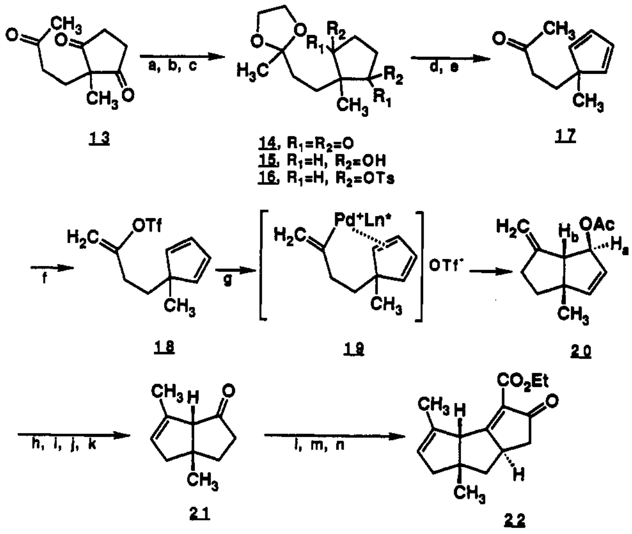
1, $R_1=R_2=R_3=R_4=H$
2, $R_1=R_3=R_4=H$, $R_2=OH$
3, $R_1=R_2=R_4=H$, $R_3=OH$
4, $R_1=R_2=R_3=H$, $R_4=OH$
5, $R_1=R_3=H$, $R_2=R_4=OH$
6, $R_2=R_4=H$, $R_1=R_3=OH$

Scheme I[a]



[a] (a) Bu_4NOH, dioxane, H_2O (74%); (b) $NaBH_4$ (100%); (c) TsCl, DMAP, pyridine (96%); (d)[15] Al_2O_3, $ClCH_2CH_2Cl$ (86%); (e) $[Pd(allyl)Cl]_2$, (*R*,*R*)-CHIRAPHOS, Bu_4NOAc, toluene (61%).

Scheme II[a]



[a] (a) $(TMSOCH_2)_2$, TMSOTf (77%); (b) $NaBH_4$ (100%); (c) TsCl, DMAP, pyridine (84%); (d) DBU (98%); (e) TsOH, acetone (88%); (f) LDA, Tf_2NPh (62%); (g) $Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc, DMSO (89%); (h) NaOMe (85%); (i) PDC, MS3A (95%); (j) CuBr, Red-Al, *s*-BuOH, THF (83%); (k) DBU (90%); (l) LDA, $ICH_2C(OMe){=}CHCO_2Et$ (85%); (m) 30% $HClO_4$, Et_2O (90%); (n) NaOEt, EtOH (85%).

We reasoned that treatment of **10** with a palladium catalyst bearing a chiral ligand in the presence of a silver salt and some oxygen nucleophile (ROH) would regioselectively afford the optically active bicyclic compound **12**, a potential intermediate for **3** and **6**, via the π-allyl intermediate **11**.[6] The regiochemistry of **12** was expected to be controlled by steric factors. The prochiral alkenyl iodide **10** was efficiently synthesized in 61% overall yield starting with **7** as shown in Scheme I. First, with the aim of application to an asymmetric synthesis, reactions utilizing (diphenylphosphino)ethane (DIPHOS) as a ligand were investigated, and it was found that exposure of **10** to Pd(OAc)$_2$ (5.8 mol %), DIPHOS (5.7 mol %), and tetrabutylammonium acetate (1.72 equiv) in CH_3CN (60 °C, 112 h) gave **12** (R = Ac) (52%) in a highly stereo- and regiocontrolled manner. The reaction did not proceed in the absence of tetrabutylammonium acetate. The stereochemical assignment for **12** followed from the ^{1}H NMR.[7] The acetate **12** was transformed into the key intermediate **21** for (±)-**3** and (±)-**6** by the sequence: (1) LiOH in aqueous THF (89%); (2) PCC–MS4A in CH_2Cl_2 (95%); (3) 10% Pd–C in 10% aqueous KOH–EtOH under H_2 (83%).[8] The spectral data of (±)-**21** thus obtained were identical with those of an authentic sample.[3] The above

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(5) For asymmetric Heck reactions, see: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Idem. *Chem. Lett.* **1990**, 1953. (c) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (d) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

(6) For a palladium-catalyzed tandem cyclization–anion capture process, see: Grigg, R.; Dorrity, M. J.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 1343 and references cited therein.

(7) J_{ab} = 0.8 Hz. Irradiation of Ha showed an enhancement of Hb (1.1%) and Hc (1.1%). J_{ab} = ca. 8 Hz is expected for the other epimer.

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synthesis is an improved synthetic route to (±)-**3** and (±)-**6** in terms of the use of a catalytic amount of $Pd(OAc)_2$.

The above reaction was next applied to a catalytic asymmetric synthesis. However, addition of a silver salt to the reaction medium, which appears to be essential to obtain a cyclized product with a high ee via a Pd^+ intermediate with a 16-electron configuration such as **19**,[5b] was found to cause the decomposition of **10**, probably owing to the presence of the cyclopentadiene moiety. For this reason, **12** (R = Ac) was obtained with only a low ee. That is, treatment of **10** with $[Pd(allyl)Cl]_2$ (10 mol %), (*R*,-*R*)-CHIRAPHOS (10 mol %), and tetrabutylammonium acetate (2.9 equiv) in toluene (60 °C, 144 h) provided **12** (R = Ac)[9] with 20% ee (61% yield).[10]

Next, we undertook a catalytic asymmetric cyclization utilizing the alkenyl triflate **18**,[11] which was expected to produce the 16-electron Pd^+ intermediate **19** efficiently even in the absence of a silver salt, leading to **20** with high ee.[5b] The prochiral alkenyl triflate **18** was readily prepared in 35% overall yield starting with **13**[12] as shown in Scheme II. Treatment of **18** with $Pd(OAc)_2$ (1.7 mol %), (*S*)-BINAP (2.1 mol %),[13] and tetrabutylammonium acetate (1.7 equiv) in DMSO at 20 °C for 2.5 h produced **20**[9] in 80% ee (89% yield).[14] The structure of **20** was determined from the ^1H NMR spectrum which showed $J_{ab} = \sim 0$ Hz. In a previous paper,[5b] we reported that an asymmetric Heck reaction of an alkenyl iodide is realtively fast when AgOAc is used, indicating that the Pd^+AcO^- intermediate is formed effectively, but the ee of the product is low. Therefore, it is noteworthy that **20** was obtained with a high ee even in the presence of excess tetrabutylammonium acetate.

The cyclized product **20** was then converted to **21**: $[\alpha]^{20}{}_D$ +532° (*c* 0.85, $CHCl_3$) (80% ee), the key intermediate for **3** and **6**, in a four-step process (60% overall yield).[3a] Furthermore, **21** was transformed into the ABC ring system **22**: $[\alpha]^{21}{}_D$ +530° (*c* 1.00, $CHCl_3$) (80% ee) in a three-step process (65% overall yield).[3b]

In conclusion, we have achieved a catalytic asymmetric synthesis of the key intermediates **21** and **22** for capnellenols by the use of the asymmetric Heck reaction followed by an anion capture process as well as an improved synthetic route to (±)-**3** and (±)-**6**. This is the first example of a catalytic asymmetric synthesis of a polycyclopentanoid.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **9**, **10**, **12**, **14**, **15**, **16**, **17**, **18**, **20**, **21**, and **22** and ^1H NMR spectra of **12** and **20** (15 pages). Ordering information is given on any current masthead page.

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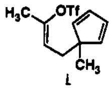
(9) Assignment of the absolute configuration was achieved by application of the CD exciton chirality method to the corresponding benzoate, and the enantiomeric excess was unequivocally determined by the ^1H NMR spectrum of the corresponding MTPA ester.

(10) Among many experiments, for example, Cl_2Pd(*R*)-BINAP in toluene affords **12** in 9% ee (63%).

(11) The use of the alkenyl triflate **i** was first planned. However, an efficient synthesis of **i** was difficult to achieve.



i

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(14) The following results were also obtained (e.g. BINAP in CH_3CN → 51% ee (51%), BINAP in dioxane → 65% ee (59%), BINAP in toluene → 26% ee (79%), BPPFA in DMSO → 26% ee (68%), BPPM in DMSO → 58% ee (61%), CHIRAPHOS in DMSO → 17% ee (44%), DIOP in DMSO → 8% ee (67%)).

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