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SYNTHETIC STUDIES ON CAPNELLOL FAMILY : AN IMPROVED SYNTHESIS OF $\Delta^{9(12)}$-CAPNELLENE-3β,8β,10α-TRIOL AND THE FIRST TOTAL SYNTHESIS OF $\Delta^{9(12)}$-CAPNELLENE-3β,8β,10α,14-TETROL

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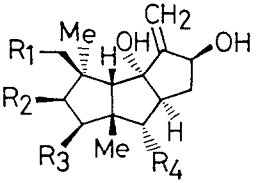
Summary : A much improved synthesis of $\Delta^{9(12)}$-capnellene-3β,8β,10α-triol and the first total synthesis of $\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetrol have been accomplished via the common synthetic intermediate **17.**



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 $R_2=R_4=H,\ R_1=R_3=OH$

Chart 1

Capnellols are sesquiterpene alcohols **1**-**6**, isolated from sun-dried colonies of the soft coral *Capnella imbricata*.[1] These substances appear to act protective roles against fish predation and invasion by microorganisms, larvae and algae.[2] Recently we have completed the first total syntheses of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol(**1**) and (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol(**3**).[3] However, the synthetic route to capnellene-triol(**3**) was quite unsatisfactory in view of the low overall yield so that we continued to study on an improved synthesis of capnellene-triol(**3**). In this communication we wish to report a much improved synthetic route to capnellene-triol(**3**) as well as the first total synthesis of the most oxygenated capnellol, (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetrol(**6**). Both syntheses utilize the common synthetic intermediate **17.**

In the previous synthesis[3] of capnellene-triol(**3**), the most unsatisfactory step was the construction of the ABC ring(**7** → **8**) probably owing to the presence of the 1α-methyl group,[4] suggesting that later introduction of the 1α-methyl group would give a more efficient route to **3** (Chart 2).

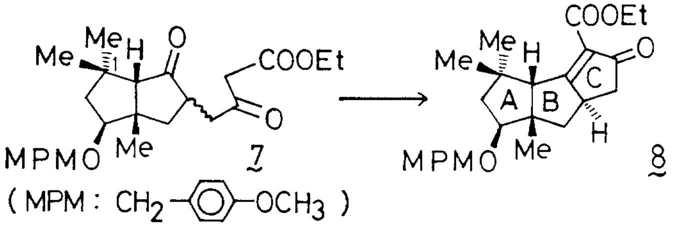
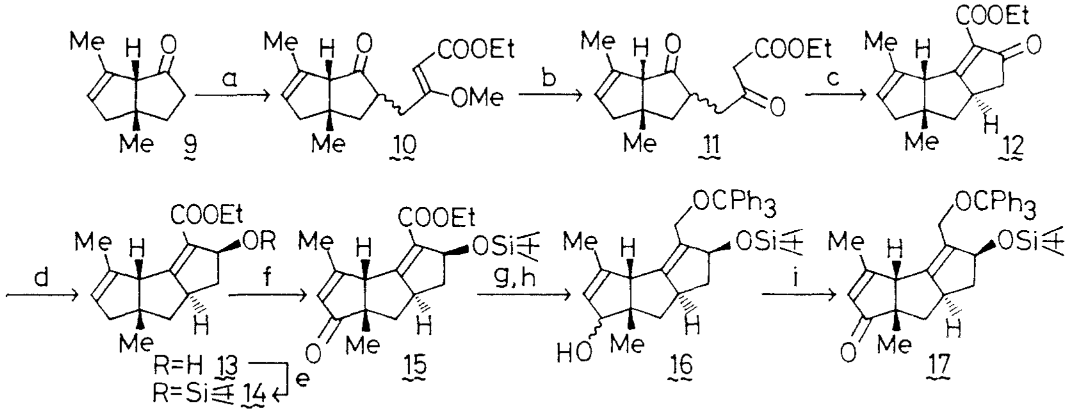


Chart 2

Reaction of the lithium enolate derived from the readily available ketone **9**[3] (LDA in THF) with ethyl 4-iodo-3-methoxycrotonate afforded **10**[5] in 85% yield as an isomeric mixture, which was converted to **11**[5] in 90% yield on exposure to 30% aqueous perchloric acid. As expected, the β-keto ester **11** was smoothly cyclized to **12**[5,6] in 85% yield just by treatment with sodium ethoxide in ethanol at room temperature. The tricyclic compound **12** was reduced to the alcohol **13**[5,7] stereospecifically with $NaBH_4$-$CeCl_3$,[8] followed by protection as TBDMS ether to give **14**[5] (75% overall yield). Allylic oxidation of **14** with CrO_3-3,5-DMP in CH_2Cl_2[9] provided the conjugated ketone **15**[5] (60%). Reduction of **15** with DIBAH and subseqent protection of the primary alcohol with Ph_3CCl-DMAP in DMF gave **16**[5] (89%), which was further converted to the versatile enone **17**[5] by treatment with activated MnO_2 in $CHCl_3$(94%)(Chart 3).

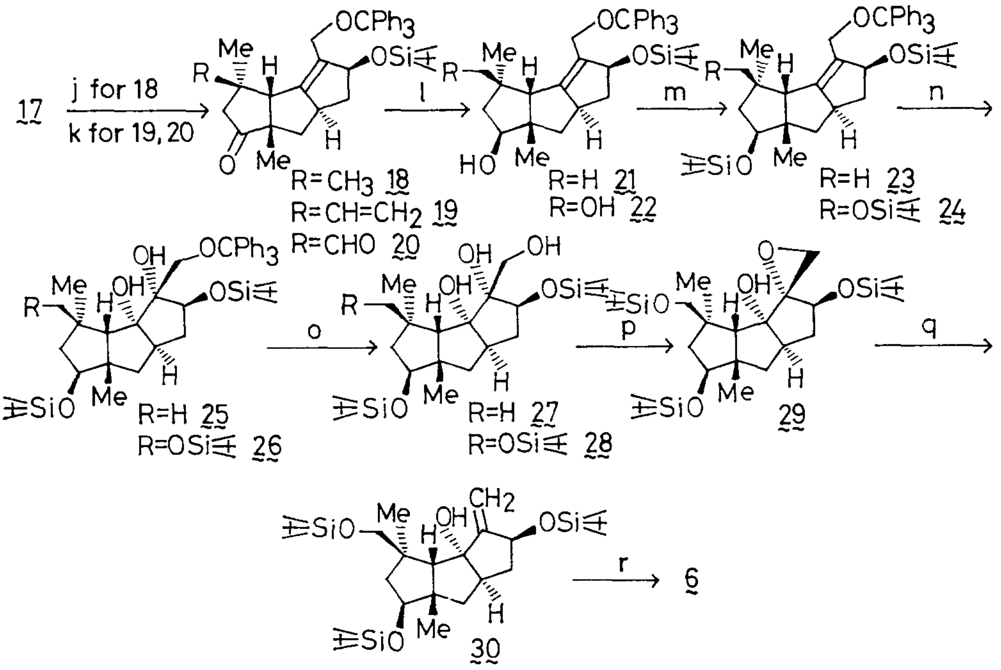


(a) LDA, $ICH_2C(OMe)=CHCOOEt$, THF, -78°-0°, 85% (b) 30%-$HClO_4$, Et_2O, r.t. 90% (c) EtONa, EtOH, r.t. 85% (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°-r.t. 70% (e) TBDMSCl, imidazole, DMF, r.t. 98% (f) CrO_3, 3,5-DMP, CH_2Cl_2, -25°, 60% (g) DIBAH, toluene, -78°-0°, 85% (h) Ph_3CCl, 4-DMAP, DMF, 70°, 95% (i) act.MnO_2, $CHCl_3$, r.t. 94%

Chart 3

With the key synthetic intermediate **17** in hand, transformation to capnellene-triol(**3**) was first attempted. Conjugate addition of Lipshutz reagent[10](higher ordered cuprate-$BF_3 \cdot OEt_2$ combination) afforded **18** in 90% yield. Reduction of **18**[5] with L-Selectride gave **21**,[5,11] which underwent silylation to furnish **23**[5] in 81% overall yield. Treatment of **23** with osmium tetroxide in pyridine followed by reductive workup provided the diol **25**[5] (82%). Chemoselective deprotection of the trityl group in **25** was performed by reaction with Et_2AlCl[12] to afford the known triol **27** (96%), whose spectral data were identical with those of an authentic sample.[3] Thus, a much improved total synthesis of capnellene-triol(**3**) has been formally completed (Chart 4).

Using the similar strategy, next we undertook the first total synthesis of capnellene-tetrol(**6**). Conjugate addition of a vinyl group, a representative



(j) $Me_2Cu(CN)Li_2$, $BF_3 \cdot Et_2O$, $THF-Et_2O$, -50°, 81% (k) $(CH_2=CH)_2Cu(CN)Li_2$, $BF_3 \cdot Et_2O$, $THF-Et_2O$, -50°, 86%, cat.OsO_4, NMO, acetone-H_2O-^tBuOH, then, $NaIO_4$, dioxane-H_2O, 80% (l) L-Selectride, THF, 0°,75% for **21**, 85% for **22** (m) TBDMSCl, imidazole, DMF, r.t. 99% for **23**, 98% for **24** (n) 3 equiv. OsO_4, pyridine, 40°, then, aq.$NaHSO_3$, 70°, 82% for **25**, 67% for **26** (o) Et_2AlCl, CH_2Cl_2, -10°, 96% for **27**, 88% for **28** (p) MsCl, NEt_3, benzene, r.t. then, DBU, r.t. 84% (q) TMSLi, HMPA-THF, -78°-r.t. 70% (r) TBAF, THF, r.t. 96%

Chart 4

hydroxymethyl equivalent, by using Lipshutz reagent[10] furnished **19**[5,13] in 86% yield, which underwent catalytic OsO_4 oxidation[14] and subsequent oxidative cleavage to give the aldehyde **20**[5] in 69% overall yield. Reduction of **20** with L-Selectride[15] followed by silylation afforded **24**[5](83% overall yield). After conversion to **26**[5](98%), chemoselective cleavage of the trityl group in **26** was best carried out by treatment with Et_2AlCl to give **28**[5] in 88% yield. Reaction of **28** with 1.2 equiv. of CH_3SO_2Cl and 1.2 equiv. of NEt_3 in benzene gave the monomesylate, which was immediately converted to the epoxide **29**[5] by treatment with DBU in 84% overall yield. Reaction of **29** with TMSLi in THF-HMPA led to **30**[5] (70%), which was followed by exposure to TBAF to provide (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetrol(**6**)(96%)(Chart 4). Spectral data of this synthetic sample were identical with those of the natural product.

In summary, the first total synthesis of (±)-**6** and a highly efficient synthesis of (±)-**3** have been accomplished by a general strategy that hopefully will allow the synthesis of other members of the capnellol family. The synthetic routes described above can provide a large amount of (±)-**3** and (±)-**6** for detailed biological studies.

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References and Notes

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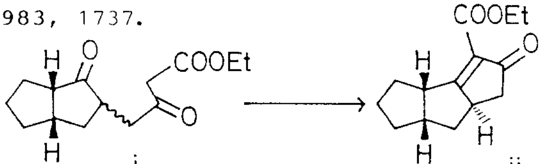
4) The aldol cyclization of the simple β-keto ester **i** afforded the tricyclic compound **ii** in an exellent yield. See: Shibasaki, M.; Mase, T.; Ikegami, S. Chemistry Lett. **1983**, 1737.



i ii

5) Satisfactory spectroscopic data were obtained for each synthetic intermediate.

6) The stereochemistry of **12** was unequivocally determined by the fact that **12** could be efficiently converted to **3** and **6**. See also ref.3.

7) The *endo*-alcohol was produced exclusively.

8) Gemal, A.L.; Luche, J.-L. J. Am. Chem. Soc. **1981**, 103, 5454.

9) Salmond, W.G.; Barta, M.A.; Havens, J.L. J. Org. Chem. **1978**, 43, 2057.

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11) A ratio of the *exo*- to *endo*-alcohol was 4.5 : 1. The *endo*-alcohol was quantitatively oxidized to **18** for recycling.

12) Köster, H.; Sinha, N.D. Tetrahedron Lett. **1982**, 23, 2641.

13) The 1β-vinyl isomer was produced exclusively.

14) The double bond at C_9-C_{10} remained intact under these reaction conditions.

15) A ratio of the *exo*- to *endo*-alcohol was 8 : 1.

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