Acknowledgment. We acknowledge the Rohm and Haas Co., the Atlantic Richfield Corporation of America, and the National Science Foundation (Grant CHE-84-06198) for generous support of this research. We thank John T. Keech for obtaining the magnetic data at the USC magnetic laboratory. Upgrade of the Divisional X-ray Diffraction Facility was supported by the National Science Foundation (Grant CHE-82-19039).

Registry No. 3, 100909-69-1; **4**, 100909-71-5; $[Co(\eta^4\text{-}\mathbf{2})(py)_2]^-$, 100909-72-6.

Supplementary Material Available: Complete details of data collection and refinement, listing of bond distances and angles, fractional atomic coordinates and Gaussian amplitudes, and structure factor amplitudes (18 pages). Ordering information is given on any current masthead page.

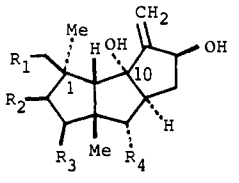
The First Total Syntheses of $\Delta^{9(12)}$-Capnellene-8β,10α-diol and $\Delta^{9(12)}$-Capnellene-3β,8β,10α-triol

Masakatsu Shibasaki,*† Toshiaki Mase,† and Shiro Ikegami‡

Sagami Chemical Research Center, Nishi-Ohnuma Sagamihara, Kanagawa 229, Japan
Faculty of Pharmaceutical Sciences, Teikyo University Sagamiko, Kanagawa 199-01, Japan

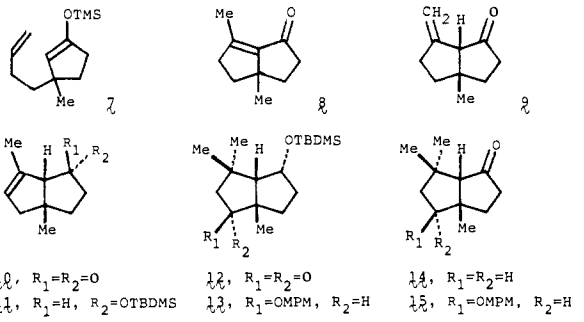
Received September 23, 1985

Capnellane is the generic name applied to the group of tricyclic sesquiterpene alcohols **1**–**6**and hydrocarbons, isolated from the soft coral *Capnella imbricata*.[1,2] These substances appear to act as chemical defense agents in the coral reef biomass to ward off algal and microbial growth and to prevent larval settlement.[3] A fascinating structural feature uniquely associated with compounds **1**–**6** is the presence of the unusual C-ring bisallylic alcohol unit, bringing about the severe steric repulsion between the hydroxyl group at C-10 and the 1α-methyl group. We describe herein the first total syntheses of (±)-**1** and (±)-**3** via the common intermediate **8**.



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

Conjugate addition to 3-methyl-2-cyclopenten-1-one using 3-butenylmagnesium bromide (2.2 molar equiv) and cuprous iodide (1.1 molar equiv) followed by quenching with chlorotrimethylsilane and triethylamine afforded **7** in 78% yield (bp 85–85.5 °C (5.5 mmHg)). Treatment of **7** with 1.0 equiv of $Pd(OAc)_2$ and 1.0 equiv of NaOAc in CH_3CN at room temperature[4] gave a mixture of **8**, **9**, and **10** in a ratio of 3.6:0.4:1 (89%).[5] The *exo*-methylene **9** was quantitatively converted to **8** on exposure to DBU in benzene at room temperature. On the other hand, treatment of the mixture (**8**–**10**) with DBU in refluxing benzene for ca. 10 h provided **10** exclusively in 94% yield. Conversion of **8** to the key intermediate **14**, needed for the synthesis of **1**, was easily achieved by reaction with Me_2CuLi (96%). Similarly, **10** was also transformed into the key intermediate **15**, required for the synthesis of **3**, by the sequence: (1) reduction of **10** with $NaBH_4$ followed by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate[6] to give **11** (84%);[7] (2) allylic oxidation of **11** with chromic anhydride and 3,5-dimethylpyrazole in CH_2Cl_2[8] and subsequent treatment with Me_2CuLi to form **12** in 60% yield (72% based on recovery of the enone); (3) reduction of **12** with Li in NH_3[9] followed by protection as the MPM (*p*-methoxybenzyl)[10] derivative to give **13** in ca. 60% yield; (4) exposure of **13** to $Bu_4N^+F^-$ and subsequent oxidation with PCC and 4A molecular sieves to provide **15** in 93% yield.



10, $R_1=R_2=O$
11, $R_1=H$, $R_2=OTBDMS$
12, $R_1=R_2=O$
13, $R_1=OMPM$, $R_2=H$
14, $R_1=R_2=H$
15, $R_1=OMPM$, $R_2=H$

With the two key synthetic intermediates in hand, the next subgoal of the synthetic effort was the efficient construction of the ABC ring systems **20** and **21**. In the first place the construction of **20** was examined. Reaction of the lithium enolate derived from **14** (LDA in THF) with ethyl 4-iodo-3-methoxycrotonate[11] gave **16** in 75% yield (83% based on recovery of **14**) as an isomeric mixture, which was converted to **18** in quantitative yield on exposure to 30% aqueous perchloric acid. The β-keto ester **18** was then subjected to the aldol cyclization. Unfortunately, all attemepts to obtain the tricyclic intermediate **20** employing a wide variety of different acidic and basic reagents met with failure. For example, under the conditions such as sodium ethoxide in ethanol at 25 °C only a trace amount of **20** was formed (<1%), **18** being recovered nearly exclusively. These results suggested that irreversible elimination reaction of the aldol derived from **18** could produce **20** in an acceptable yield. We speculated that β-silyloxy ketones may undergo irreversible elimination to conjugated ketones in the presence of trimethylsilyl trifluoromethanesulfonate, giving hexamethyldisiloxane which was expected not to undergo Michael addition to conjugated ketones. This expectation was fully realized and led to success. Thus, treatment of **18** with 3 molar equiv of trimethylsilyl trifluoromethanesulfonate and 2 molar equiv of triethylamine in refluxing benzene for 10 h afforded **20** in 42% yield together with recovery of **18** in ca. 32%. Since recovered **18** was again used for the cyclization reaction,[12] this novel conditions provided **20** in greater than 50% yield after two cycles.

† Sagami Chemical Research Center.
‡ Teikyo University.

(1) (a) Kaisin, M.; Sheikh, Y. M.; Durham, L. J.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J. C.; Losman, D.; Karlsson, R. *Tetrahedron Lett.* **1974**, 2239. (b) Sheikh, Y. M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J. C. *Tetrahedron* **1976**, *32*, 1171. (c) Sheikh, Y. M.; Djerassi, C.; Braekman, J. C.; Daloze, D.; Kaisin, M.; Tursch, B.; Karlsson, R. *Tetrahedron* **1977**, *33*, 2115. (d) Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978**, 1651.

(2) For syntheses of the parent hydrocarbon, (±)-$\Delta^{9(12)}$-capnellene, see: (a) Paquette, L. A.; Stevens, K. E. *Tetrahedron Lett.* **1981**, *22*, 4393. (b) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981**, *22*, 4389. Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928. (c) Oppolzer, W.; Bättig, K. *Tetrahedron Lett.* **1982**, *23*, 4669. (d) Huguet, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 2413. (e) Mehta, G.; Reddy, D. S.; Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824. (f) Piers, E.; Karunaratne, V. *Can. J. Chem.* **1984**, *62*, 629. (g) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

(3) (a) Ciereszko, L. S. *Tra. N. Y. Acad. Sci.* **1962**, *24*, 502. (b) Burkolder, P. R.; Burkolder, L. M. *Science (Washington, D.C.)* **1958**, *127*, 1174. (c) Ciereszko, L. S.; Karns, T. K. B. In *Biology and Geology of Coral Reefs*; Jones, O. A., Endean, R., Eds.; Academic Press: New York, 1972; Vol. 2, Chapter 6.

(4) Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 4519.

(5) Aldol reaction of 3-methyl-3-(3-oxobutyl)cyclopentanone afforded the bicyclo[3.2.1]octane ring system exclusively.

(6) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(7) At the reduction stage a small amount of the exo alcohol, which was easily oxidized to **10** for recycling, was formed.

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

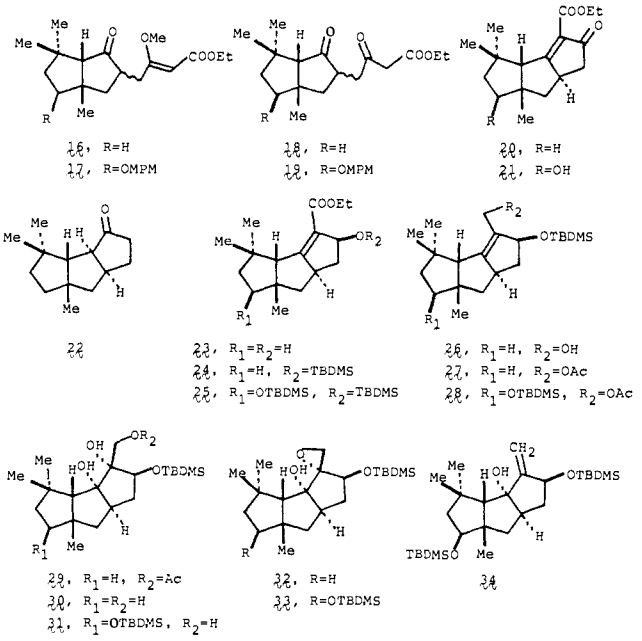
(9) A ratio of the exo- to endo alcohol was ca. 3:2. The endo alcohol was quantitatively oxidized to **12** for recycling.

(10) Oikawa, Y.; Yoshida, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(11) Danishefsky, S.; Vaugham, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.

(12) It was necessary to treat recovered **18** with sodium ethoxide in EtOH before the aldol cyclization.

0002-7863/86/1508-2090$01.50/0



The stereochemistry of **20** was unequivocally determined by converting to the known **22**.[2b]

Likewise the intermediate **21** was also obtained in ca. 20% overall yield from **15** by using the above strategy. Under the cyclization conditions deprotection of the MPM group occurred simultaneously to give **21**.

Transformation of **20** to (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**) was first investigated. Reduction of **20** with $NaBH_4$–$CeCl_3$[13] gave **23** exclusively,[14] which underwent silylation (*tert*-butyldimethylsilyl chloride and imidazole) to give **24** in 98% overall yield. DIBAH reduction of **24** (63%) followed by acetylation (92%) provided **27**. The acetate **27** was then converted to **29** in 94% yield on exposure to 2.5 equiv of osmium tetraoxide in pyridine at 30 °C for 14 h followed by reducitve workup (saturated aqueous $NaHSO_3$, 50 °C for 9 h). Treatment of **29** with K_2CO_3 in MeOH gave **30** (98%). Reaction of **30** with 1.2 equiv of CH_3SO_2Cl and 1.2 equiv of triethylamine in CH_2Cl_2 gave the monomesylate, which was immediately converted to **32** by treatment with DBU in benzene (98% overall yield). Reaction of **32** with (trimethylsilyl)lithium in HMPA–THF followed by exposure to $Bu_4N^+F^-$ provided (±)-**1** in 53% yield, whose spectral data were identical with those reported (^1H NMR, IR, mass).[1,15]

With the first total synthesis of **1** completed, we next investigated the total synthesis of (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**3**) using similar strategy. Reduction of **21** with $NaBH_4$-$CeCl_3$ followed by silylation gave **25** in a good yield. DIBAH reduction and subsequent acetylation afforded **28**, which was then converted to **31** in a two-step process (OsO_4, then K_2CO_3 in MeOH) (ca. 35% overall yield from **25**). Epoxide formation (88%) followed by treatment with (trimethylsilyl)lithium gave **34** (75%). Exposure to $Bu_4N^+F^-$ in THF accomplished the first total synthesis of (±)-**3** (78%), whose spectal data were identical with those reported.[1] Furthermore the spectral data of $\Delta^{9(12)}$-8-oxocapnellene-3β,10α-diol derived from **3** by MnO_2 oxidation were also identical with those reported.[1]

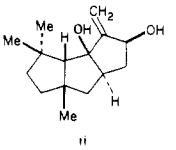
In summation, the first total syntheses of (±)-**1** and (±)-**3** have been accomplished by a general strategy that hopefully will allow the synthesis of other members of the capnellane family. The novel TMSOTf–Et_3N-induced aldol cyclizations of keto esters developed during these syntheses are expected to find other applications in complex synthetic situation and are under further exploration. Biological investigations with **1**, **3**, and related compounds as well as asymmetric approaches to these natural products are currently in progress.

Supplementary Material Available: Full NMR data for compounds **8–21**, **23–34**, and **ii** (3 pages). Ordering information is given on any current masthead page.

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

(14) The stereochemistry of **23** was unequivocally proven by the fact that **23** was converted to **1** without producing the 8-epimer of **1** (i). For the synthesis of i, see: Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1983**, *23*, 547.

(15) Another route to (±)-**1** from **26** [(i) CCl_4–HMPT, (ii) Me_3SiLi in HMPA–THF, (iii) *m*-CPBA, (iv) $Bu_4N^+F^-$) was also investigated. However, surprisingly, this synthetic route provided the bisallylic alcohol ii in 38% overall yield from **26**. The structure of ii was presumed to be the 10-epimer of **1** on



ii

the basis of the mass and ^1H NMR. The X-ray crystallographic analysis is under way.

Cobalt-Mediated [2 + 2 + 2] Cycloadditions of Alkynes to the Indole 2,3-Double Bond: An Extremely Facile Entry into the Novel 4a,9a-Dihydro-9*H*-carbazole Nucleus

Douglas B. Grotjahn and K. Peter C. Vollhardt*

Department of Chemistry, University of California Berkeley, and the Materials and Molecular Research Division, Lawrence Berkeley Laboratory Berkeley, California 94720

Received December 16, 1985

Because of the extremely diverse physiological activity exhibited by the indole nucleus[1] and its presence in a multitude of natural products[2] selective alteration of its structure has commanded a considerable amount of synthetic attention. Part of this effort has involved the utilization of the 2,3-double bond in Diels–Alder[3] and other cycloadditions.[4] We report a novel mode of reactivity of this bond in the presence of η^5-CpCo reagents: the [2 + 2 + 2] cycloaddition to two alkynes to provide the hitherto unknown[5] 4a,9a-dihydro-9*H*-carbazole nucleus as incorporated in a variety of complex polycyclic dienes. This methodology demonstrates for the first time the feasibility of activating aromatic double bonds in CpCo-mediated cyclizations[6] and provides a powerful means by which to fuse several rings onto the indole moiety in one step.

The starting materials **1** were prepared in one or two steps from known indole derivatives by adaptation of literature procedures,[7–9] using the appropriate acyl chloride[10a–c] or iodoalkane (Table I).[10d]

(1) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Durg Synthesis*; Wiley-Interscience: New York, 1977, 1980, 1984; Vol. 1–3.

(2) (a) Herbert, R. B. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley-Interscience: New York, 1983; Vol. 25, Part 4, Chapter 1. (b) *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zank, N. H., Eds.; Academic Press: New York, 1980. (c) *The Indoles: the Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983. (d) "New Developments in Indole Alkaloids"; *Tetrahedron Symposia in print*, 12; Kuehne, M. E., Ed.; *Tetrahedron* **1983**, *39* (22), 1983.

(3) Jones, R. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Reese, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, p 201.

(4) (a) Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem.* **1978**, *23*, 263. (b) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(5) Joule, J. A. *Adv. Heterocycl. Chem.* **1984**, *35*, 83.

(6) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.

(7) N-Alkylation: Kikugawa, Y.; Mikaye, U. *Synthesis* **1981**, 461.

(8) N-Acylation: Kikugawa, Y. *Synthesis* **1981**, 460.

(9) (a) DeSilva, S. O.; Snieckus, V. *Can. J. Chem.* **1978**, *56*, 1621. (b) Alemany, A.; Alvarez, E. F.; Lopez, O. N.; Herraez, M. E. R. *Bull. Soc. Chim. Fr.* **1974**, 2883.

0002-7863/86/1508-2091$01.50/0