Total Synthesis of the Tetraquinane Diterpenoid (±)-Crinipellin B

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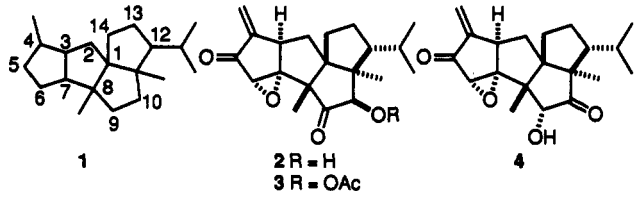
Summary: Beginning with 2-methyl-2-cyclopenten-1-one (**5**), the total synthesis of the structurally novel tetraquinane diterpenoid (±)-crinipellin B (**4**) has been accomplished via a 22-step sequence of reactions.

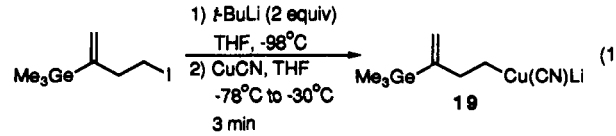
The crinipellane-type diterpenoids are a small family of structurally unprecedented natural products that share the 12-isopropyl-4,8,11-trimethyltetracyclo[6.6.0.0^{1,11}.0^{3,7}]-tetradecane skeleton **1**.[1] Three members of this group, crinipellin A, *O*-acetylcrinipellin A, and crinipellin B, isolated from different strains of the fungus *Crinipellis stipitaria* (Agaricales), have been shown to possess the structures shown in formulas **2**–**4**, respectively.[1] Each of these highly oxygenated substances contains eight stereogenic centers, three of which consist of contiguous quaternary chiral carbon atoms (C-1, C-8, C-11). Compounds **2**–**4** exhibit interesting biological properties, including powerful antibiotic activity.[1,2]



A number of reports describing synthetic approaches to the crinipellins have appeared.[3] However, to our knowledge, the total synthesis of one or more of these substances has not yet been recorded. We describe herein a total synthesis of (±)-crinipellin B via a route in which two new 5-membered ring annulation methods play key roles.

Conversion of the enone **5** into the functionalized tetraquinane **18** was achieved via the reaction sequence summarized in Scheme I. Copper(I)-catalyzed conjugate addition of *i*-PrMgBr to **5** in the presence of Me_3SiCl and HMPA provided the enol silyl ether **6**.[4] As expected (steric approach control), alkylation of the lithium enolate derived from **6** with 2-(bromomethyl)-1-butene in the presence of $(Ph_3P)_4Pd$[5] gave, stereoselectively, the monoalkylated product **7**, along with minor amounts of dialkylated materials. Base-promoted cyclization of the dione **8**, which was readily obtained by oxidative cleavage of the alkene function in **7**,[6] produced the bicyclic enone **9** in excellent yield.

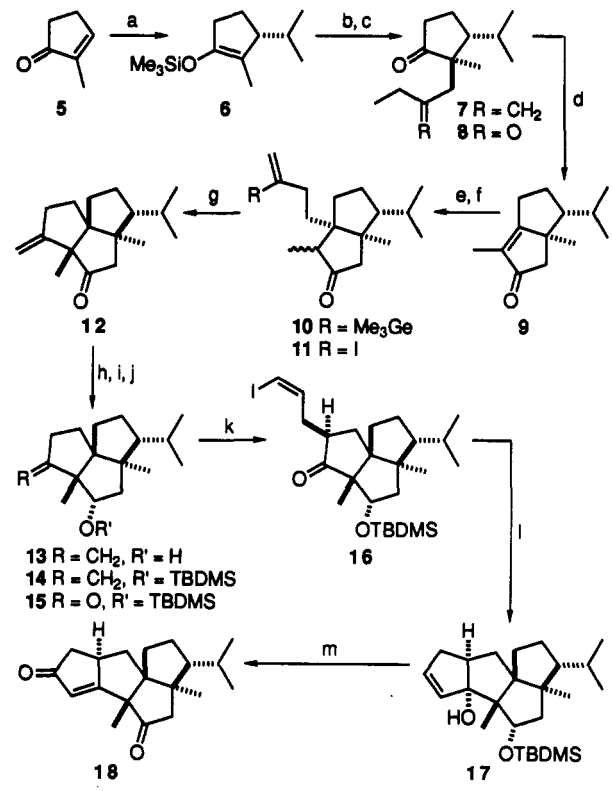
Transformation of **9** into the triquinane **12** made use of a new annulation sequence developed recently in our laboratory.[7] Thus, conjugate addition of the novel cuprate reagent **19** (see eq 1) to the enone **9** in the presence of



(1)

Me_3SiBr, followed by appropriate workup, afforded the keto trimethylgermane **10** (mixture of epimers), which was

Scheme I[a]



[a] (a) *i*-PrMgBr, CuBr·Me_2S, Me_3SiCl, HMPA, THF, −78 °C, 4 h; Et_3N (94%); (b) MeLi, THF, 0 °C; 2-(bromomethyl)-1-butene, $(Ph_3P)_4Pd$, THF, −20 °C, 2 h; 0 °C, 5 h (76%); (c) O_3, MeOH–CH_2Cl_2, −78 °C; Me_2S, −78 °C to room temperature; concentrate mixture, add 10% HCl–H_2O and THF, stir at room temperature for 18 h (93%); (d) MeONa, MeOH, reflux 15 h (97%); (e) reagent **19**, Me_3SiBr, THF, −78 °C, 8 h; −48 °C, 2 h (83%); (f) I_2, CH_2Cl_2, room temperature, 16 h (98%); (g) $(Ph_3P)_4Pd$ (21 mol %), *t*-BuOK, *t*-BuOH, THF, room temperature (84%); (h) *n*-Bu(*i*-Bu)$_2$Al(H)Li, Et_2O, −78 °C, 2 h; 0 °C, 1 h (93%); (i) *t*-Bu$Me_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, −78 °C, 75 min; 0 °C, 20 min (98%); (j) OsO_4, C_5H_5N, room temperature, 23 h; $NaHSO_3$, H_2O, 1 h; $Pb(OAc)_4$, THF, 0 °C, 30 min; $HOCH_2CH_2OH$, 10 min (93%); (k) *i*-Pr_2NLi, THF, −78 °C; (*Z*)-3-bromo-1-iodopropene, room temperature, 7.5 h (76%); (l) *n*-BuLi (2.5 equiv), THF, −78 °C, 110 min (93%); (m) C_5H_5N·CrO_3·HCl, CH_2Cl_2, Celite, room temperature, 3.5 h (51%).

(1) Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 709.
(2) Kupka, J.; Anke, T.; Oberwinkler, F.; Schramm, G.; Steglich, W. *J. Antibiot.* **1979**, *32*, 130.
(3) Mehta, G.; Rao, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1578. Mehta, G.; Rao, K. S.; Reddy, M. S. *Tetrahedron Lett.* **1988**, *29*, 5025. Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272. Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 693.
(4) All new compounds were spectroscopically characterized and gave satisfactory elemental analyses and/or high-resolution mass spectrometric molecular mass determinations.
(5) Negishi, E.; John, R. A. *J. Org. Chem.* **1983**, *48*, 4098.
(6) The ^1H NMR spectrum of the crude product acquired from subjection of **7** to ozonolysis–Me_2S (step c, Scheme I) showed MeO signals, indicating the presence of a ketal function. Acid hydrolysis of this material produced **8** in high yield.
(7) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454.

0022-3263/93/1958-0011$04.00/0

converted smoothly into the corresponding keto iodide **11**. An efficient Pd(0)-catalyzed cyclization of **11** in the presence of *t*-BuOK[7] gave **12**. The overall conversion of **5** into **12** was highly stereoselective and produced a functionalized tricycle in which the three contiguous quaternary stereogenic centers required for the eventual synthesis of (±)-crinipellin B (**4**) had been installed cleanly and efficiently.

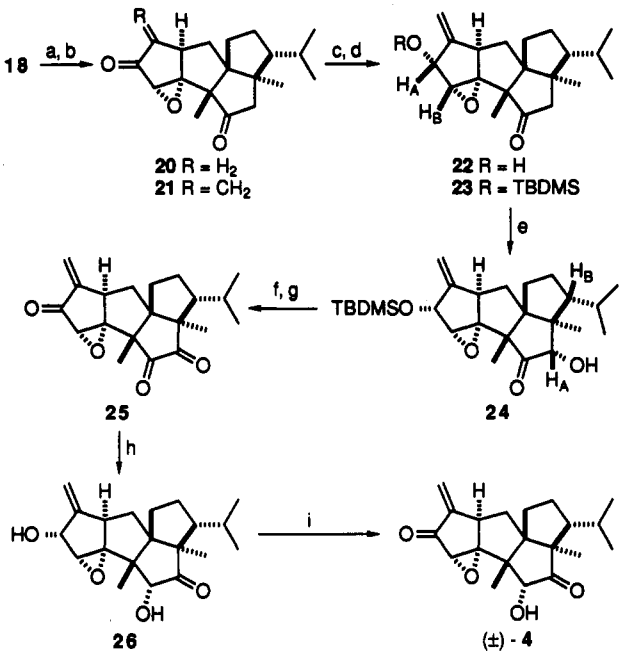
A straightforward sequence of reactions served to effect the efficient conversion of **12** into the keto ether **15** (mp 47–48.5 °C), via the intermediates **13** and **14**. Of particular note was the highly stereoselective reduction of **12** with the complex metal hydride derived from reaction of *i*-Bu_2AlH with *n*-BuLi.

Construction of the fourth required 5-membered ring was initially problematic. Although a number of known cyclopentenone annulation methods[8] were attempted, none were successful. In the present case, the usual difficulties associated with the conversion of (unsymmetrically substituted) cyclopentanones into the corresponding bicyclo[3.3.0]oct-1-en-3-ones are exacerbated by the hindered nature of the carbonyl function in **15**. In view of these difficulties, a new cyclopentenone annulation sequence was developed (transformation of **15** into **18**, Scheme I).[9]

Alkylation of **15** with (*Z*)-3-bromo-1-iodopropene[10] was highly stereoselective and provided the keto iodide **16** efficiently. Treatment of **16** with *n*-BuLi in THF at −78 °C[11] produced, in excellent yield, the allylic alcohol **17** (mp 61.5–63 °C). Completion of the necessary annulation sequence required oxidative rearrangement of **17** with a Cr(VI) reagent. Interestingly, treatment of **17** with excess PCC in the presence of Celite[12] produced, as the major product,[13] the keto enone **18** (mp 130–131.5 °C). Thus, in addition to effecting the expected process (cyclopentenone formation), this reaction also caused oxidative conversion of the silyl ether function into the corresponding carbonyl group.

Completion of the synthesis of (±)-**4** was carried out as summarized in Scheme II. The epoxide **20**, readily derived from **18**, was treated sequentially with $(Me_3Si)_2NLi$ and dimethyl(methylene)ammonium iodide.[14] Flash chromatography of the resultant amino ketone effected elimination of Me_2NH and produced the enone **21**[15] (mp 157.5–158.5 °C). Thus, the stereoselective construction of the

Scheme II[a]



[a] (a) H_2O_2, $NaHCO_3$, H_2O–THF (1:2), room temperature, 55 min (84%); (b) $(Me_3Si)_2NLi$, THF, −78 °C; $(H_2C{=}NMe_2)^+I^-$, −78 °C, 70 min; −70 °C, 18 min; flash chromatography (silica gel) (78%); (c) $NaBH_4$, MeOH–THF, −78 °C, 85 min; −63 °C, 15 min (80%); (d) *t*-$BuMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, −78 °C, 2 h; 0 °C, 70 min (88%); (e) $(Me_3Si)_2NK$, THF, −78 °C; 2-(phenylsulfonyl)-3-phenyloxaziridine, −78 °C, 45 min (68%); (f) *n*-Bu_4NF, THF, room temperature, 75 min; (g) Dess–Martin periodinane reagent (ref 18) (4 equiv), C_5H_5N (2 equiv), CH_2Cl_2, room temperature; $Na_2S_2O_3$, $NaHCO_3$, H_2O (44% from **24**); (h) *n*-Bu(*i*-Bu)$_2$Al(H)Li (4.6 equiv), Et_2O–THF, −78 °C, 30 min (41%); (i) C_5H_5N-SO_3, Me_2SO, Et_3N, CH_2Cl_2, room temperature, 9.5 h (49%).

complete carbon skeleton of (±)-crinipellin B (**4**) had been achieved. Intermediate **21** was smoothly transformed, via the alcohol **22**[16] (mp 146–147.5 °C), into the silyl ether **23** (mp 187–188.5 °C). The last required oxygen function was introduced by hydroxylation[17] of the potassium enolate of **23**, a process that afforded, stereoselectively, the α-hydroxy ketone **24**[16] (mp 190.5–192 °C). It may be noted that **24** possesses the relative configuration at C-10 opposite to that present in crinipellin A (**2**).

Cleavage of the silyl ether function in **24**, followed by immediate oxidation[18] of the resultant product, gave the triketone **25** (yellow-orange needles, mp 188–189.5 °C). Attempts to effect chemoselective reduction of only the C-9 carbonyl group in **25** were not successful. However, low-temperature reduction of this material with *n*-Bu(*i*-Bu)$_2$Al(H)Li provided the keto diol **26**[19] as the major product, along with less polar (TLC) byproducts. Oxidation[20] of **26** afforded, in addition to some starting material (12%) and a minor byproduct, (±)-crinipellin B (**4**). This substance (mp 153.5–155 °C) exhibited spectra in full accord with structural formula **4**, and its ^{1}H NMR

(8) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry (Reactivity and Structure Concepts in Organic Chemistry)*; Springer-Verlag: Berlin, 1987; Vol. 26. Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467.

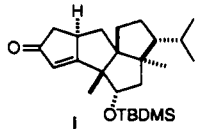
(9) The generality of this new, potentially useful method is currently under investigation.

(10) This substance was prepared by reduction (*i*-Bu_2AlH, THF) of methyl (*Z*)-3-iodopropenoate (Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709), followed by reaction of the resultant alcohol with Ph_3PBr_2 in CH_2Cl_2.

(11) Cf. Piers, E.; Marais, P. C. *Tetrahedron Lett.* **1988**, *29*, 4053.

(12) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352.

(13) Minor products from this oxidation were **i** and the diketo epoxide **20** (see Scheme II). Interestingly, **i** did not undergo epoxidation when treated with H_2O_2 in the presence of base (Scheme II, step a).



i

(14) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(15) The structure of **21**, and thereby of previous intermediates in the synthetic sequence, was confirmed by an X-ray crystallographic study. We are grateful to Dr. S. J. Rettig for carrying out this structure determination. Details will be reported elsewhere.

(16) The relative configuration of the newly introduced stereogenic center of this substance was confirmed by ^{1}H NMR spectroscopy. Thus, in nuclear Overhauser enhancement difference experiments, irradiation of H_A (δ 4.52 for **22**, 4.04 for **24**) caused enhancement of the signals due to H_B (δ 3.52 for **22**, 1.27–1.37 (m) for **24**).

(17) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

spectrum was found to be identical with that of natural (−)-crinipellin B.[21]

In summary, a 22-step conversion of 2-methyl-2-cyclopenten-1-one (**5**) into (±)-crinipellin B (**4**) was achieved. Two new annulation methods developed in our laboratory played important roles in the assembly of the required tetraquinane carbon skeleton (see conversions **9** into **12** and **15** into **18**).

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Supplementary Material Available: Experimental procedures for the preparation and ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compounds **6–18**, **20–26**, and (±)-**4**, experimental details of the X-ray crystallographic study on intermediate **21**, and a stereoview of this substance (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) The overall conversion of **24** into **26** could also be achieved as follows: (i) oxidation of **24** with tetra-*n*-propylammonium perruthenate and *N*-methylmorpholine *N*-oxide in CH_2Cl_2 (Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13) (74%); (ii) silyl ether cleavage with *n*-Bu_4NF in THF (68%); (iii) reduction of the C-9 carbonyl group with *n*-Bu-(*i*-Bu)$_2$Al(H)Li in Et_2O–THF (53%). Although this sequence was somewhat more efficient than that summarized in Scheme II, the intermediates were quite unstable and, therefore, were difficult to purify and completely characterize.

(20) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(21) We are very grateful to Professor W. Steglich for sending us a copy of the ^{1}H NMR spectrum of natural (−)-crinipellin B.